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(54) Title: HETEROCYCLIC MODULATORS OF NUCLEAR RECEPTORS

(57) Abstract: Compounds, compositions and methods for modulating the activity of nuclear receptors are provided. In particular, heterocyclic compounds are provided for modulating the activity of farnesoid X receptor (FXR), liver X receptor (LXR) and/or orphan nuclear receptors. In certain embodiments, the compounds are thiazolidinone derivatives.

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## HETEROCYCLIC MODULATORS OF NUCLEAR RECEPTORS RELATED APPLICATION

Benefit of priority under 35 U.S.C. 119(e) is claimed herein to U.S. provisional patent application No. 60/342,720, filed December 21, 2001, to

- 5 Martin *et al.*, entitled "HETEROCYCLIC MODULATORS OF NUCLEAR RECEPTORS." The disclosure of the above-referenced application is incorporated by reference herein in its entirety.

### FIELD

- Compounds, compositions and methods for modulating the activity of  
10 nuclear receptors are provided. In particular, heterocyclic compounds are provided for modulating the activity of orphan nuclear receptors.

### BACKGROUND

#### Nuclear Receptors

- Nuclear receptors are a superfamily of regulatory proteins that are  
15 structurally and functionally related and are receptors for, *e.g.*, steroids, retinoids, vitamin D and thyroid hormones (see, *e.g.*, Evans (1988) *Science* 240:889-895). These proteins bind to cis-acting elements in the promoters of their target genes and modulate gene expression in response to ligands for the receptors.

- 20 Nuclear receptors can be classified based on their DNA binding properties (see, *e.g.*, Evans, *supra* and Glass (1994) *Endocr. Rev.* 15:391-407). For example, one class of nuclear receptors includes the glucocorticoid, estrogen, androgen, progestin and mineralocorticoid receptors which bind as homodimers to hormone response elements (HREs) organized as inverted  
25 repeats (see, *e.g.*, Glass, *supra*). A second class of receptors, including those activated by retinoic acid, thyroid hormone, vitamin D<sub>3</sub>, fatty acids/peroxisome proliferators (*i.e.*, peroxisome proliferator activated receptor (PPAR)) and ecdysone, bind to HREs as heterodimers with a common  
30 partner, the retinoid X receptors (*i.e.*, RXRs, also known as the 9-*cis* retinoic acid receptors; see, *e.g.*, Levin *et al.* (1992) *Nature* 355:359-361 and Heyman *et al.* (1992) *Cell* 68:397-406).

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RXRs are unique among the nuclear receptors in that they bind DNA as a homodimer and are required as a heterodimeric partner for a number of additional nuclear receptors to bind DNA (see, e.g., Mangelsdorf *et al.* (1995) *Cell* 83:841-850). The latter receptors, termed the class II nuclear receptor subfamily, include many which are established or implicated as important regulators of gene expression. There are three RXR genes (see, e.g., Mangelsdorf *et al.* (1992) *Genes Dev.* 6:329-344), coding for RXR $\alpha$ , - $\beta$ , and - $\gamma$ , all of which are able to heterodimerize with any of the class II receptors, although there appear to be preferences for distinct RXR subtypes by partner receptors *in vivo* (see, e.g., Chiba *et al.* (1997) *Mol. Cell. Biol.* 17:3013-3020). In the adult liver, RXR $\alpha$  is the most abundant of the three RXRs (see, e.g., Mangelsdorf *et al.* (1992) *Genes Dev.* 6:329-344), suggesting that it might have a prominent role in hepatic functions that involve regulation by class II nuclear receptors. See also, Wan *et al.* (2000) *Mol. Cell. Biol.* 20:4436-4444.

#### 15 Orphan Nuclear Receptors

Included in the nuclear receptor superfamily of regulatory proteins are nuclear receptors for whom the ligand is known and those which lack known ligands. Nuclear receptors falling in the latter category are referred to as orphan nuclear receptors. The search for activators for orphan receptors has led to the discovery of previously unknown signaling pathways (see, e.g., Levin *et al.*, (1992), *supra* and Heyman *et al.*, (1992), *supra*). For example, it has been reported that bile acids, which are involved in physiological processes such as cholesterol catabolism, are ligands for FXR (*infra*).

Since it is known that products of intermediary metabolism act as transcriptional regulators in bacteria and yeast, such molecules may serve similar functions in higher organisms (see, e.g., Tomkins (1975) *Science* 189:760-763 and O'Malley (1989) *Endocrinology* 125:1119-1120). For example, one biosynthetic pathway in higher eukaryotes is the mevalonate pathway, which leads to the synthesis of cholesterol, bile acids, porphyrin, dolichol, ubiquinone, carotenoids, retinoids, vitamin D, steroid hormones and farnesylated proteins.



**FXR**

- FXR (originally isolated as RIP14 (retinoid X receptor-interacting protein-14), see, e.g., Seol *et al.* (1995) *Mol. Endocrinol.* 9:72-85) is a member of the nuclear hormone receptor superfamily and is primarily
- 5 expressed in the liver, kidney and intestine (see, e.g., Seol *et al.*, *supra* and Forman *et al.* (1995) *Cell* 81:687-693). It functions as a heterodimer with the retinoid X receptor (RXR) and binds to response elements in the promoters of target genes to regulate gene transcription. The FXR-RXR heterodimer binds with highest affinity to an inverted repeat-1 (IR-1) response element, in which
- 10 consensus receptor-binding hexamers are separated by one nucleotide. FXR is part of an interrelated process, in that FXR is activated by bile acids (the end product of cholesterol metabolism) (see, e.g., Makishima *et al.* (1999) *Science* 284:1362-1365, Parks *et al.* (1999) *Science* 284:1365-1368, Wang *et al.* (1999) *Mol. Cell.* 3:543-553), which serve to inhibit cholesterol catabolism.
- 15 See also, Urizar *et al.* (2000) *J. Biol. Chem.* 275:39313-39317.

**LXR $\alpha$  and LXR $\beta$** 

- LXR $\alpha$  is found predominantly in the liver, with lower levels found in kidney, intestine, spleen and adrenal tissue (see, e.g., Willy, *et al.* (1995) *Gene Dev.* 9(9):1033-1045). LXR $\beta$ , also known as UR (ubiquitous receptor),
- 20 is ubiquitous in mammals and was found in nearly all tissues examined. LXRs are activated by certain naturally occurring, oxidized derivatives of cholesterol (see, e.g., Lehmann, *et al.* (1997) *J. Biol. Chem.* 272(6):3137-3140). LXR $\alpha$  is activated by oxysterol and promotes cholesterol metabolism (Peet *et al.* (1998) *Cell* 93:693-704). Thus, LXRs appear to play a
- 25 role in, e.g., cholesterol metabolism (see, e.g., Janowski, *et al.* (1996) *Nature* 383:728-731).

**Nuclear Receptors and Disease**

- Nuclear receptor activity has been implicated in a variety of diseases and disorders, including, but not limited to, hypercholesterolemia (see, e.g.,
- 30 International Patent Application Publication No. WO 00/57915), osteoporosis and vitamin deficiency (see, e.g., U.S. Patent No. 6,316,5103),

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- hyperlipoproteinemia (see, e.g., International Patent Application Publication No. WO 01/60818), hypertriglyceridemia, lipodystrophy, peripheral occlusive disease, ischemic stroke, hyperglycemia and diabetes mellitus (see, e.g., International Patent Application Publication No. WO 01/82917),
- 5 atherosclerosis and gallstones (see, e.g., International Patent Application Publication No. WO 00/37077), disorders of the skin and mucous membranes (see, e.g., U.S. Patent Nos. 6,184,215 and 6,187,814, and International Patent Application Publication No. WO 98/32444), acne (see, e.g., International Patent Application Publication No. WO 00/49992), and cancer,
- 10 Parkinson's disease and Alzheimer's disease (see, e.g., International Patent Application Publication No. WO 00/17334). Activity of nuclear receptors, including FXR, LXRs and/or orphan nuclear receptors, has been implicated in physiological processes including, but not limited to, bile acid biosynthesis, cholesterol metabolism or catabolism, and modulation of cholesterol 7 $\alpha$ -
- 15 hydroxylase gene (CYP7A1) transcription (see, e.g., Chiang *et al.* (2000) *J. Biol. Chem.* 275:10918-10924), HDL metabolism (see, e.g., Urizar *et al.* (2000) *J. Biol. Chem.* 275:39313-39317), hyperlipidemia, cholestasis, and increased cholesterol efflux and increased expression of ATP binding cassette transporter protein (ABC1) (see, e.g., International Patent Application
- 20 Publication No. WO 00/78972).

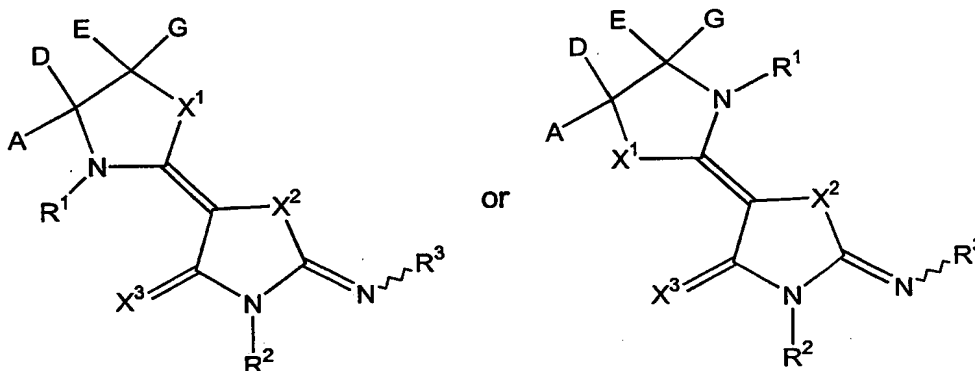
Thus, there is a need for compounds, compositions and methods of modulating the activity of nuclear receptors, including FXR, LXRs and/or orphan nuclear receptors. Such compounds are useful in the treatment, prevention, or amelioration of one or more symptoms of diseases or disorders

25 in which nuclear receptor activity is implicated.

## SUMMARY

Compounds for use in compositions and methods for modulating the activity of nuclear receptors are provided. In particular, compounds for use in compositions and methods for modulating farnesoid X receptor (FXR), liver X receptors (LXR $\alpha$  and LXR $\beta$ ) and/or orphan nuclear receptors, are provided. In certain embodiments, the compounds are heterocyclic compounds that are substituted with a heterocyclylene group and an imine moiety. In one embodiment, the compounds provided herein are agonists of FXR and/or LXR. In another embodiment, the compounds provided herein are antagonists of FXR and/or LXR. Agonists that exhibit low efficacy are, in certain embodiments, antagonists.

In one embodiment, the compounds for use in the compositions and methods provided herein have formulae I:



or a pharmaceutically acceptable derivative thereof, where A, D, E and G are selected from (i) or (ii) as follows:

- (i) A and G are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted

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- heteroarylium, substituted or unsubstituted heteroaryliumalkyl, halo, pseudohalo,  $OR^{10}$ ,  $SR^{10}$ ,  $S(=O)R^{13}$ ,  $S(=O)_2R^{13}$ ,  $NR^{11}R^{12}$  and  $C(=J)R^{13}$ , or A and G together form substituted or unsubstituted alkylene, substituted or unsubstituted azaalkylene, substituted or unsubstituted oxaalkylene, substituted or unsubstituted thiaalkylene, substituted or unsubstituted alkenylene, substituted or unsubstituted alkynylene, substituted or unsubstituted 1,3-butadienylene, substituted or unsubstituted 1-aza-1,3-butadienylene, or substituted or unsubstituted 2-aza-1,3-butadienylene;
- 10 D and E are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo and pseudohalo or D and E together form a bond; or
- 15 (ii) A and D; or E and G; together form substituted or unsubstituted alkylene, substituted or unsubstituted azaalkylene, substituted or unsubstituted oxaalkylene, or substituted or unsubstituted thiaalkylene; and the others of A, D, E and G are selected as in (i);
- 20  $X^1$  and  $X^2$  are each independently selected from O, S,  $S(=O)$ ,  $S(=O)_2$ , Se,  $NR^5$ ,  $CR^6R^7$  and  $CR^8=CR^9$ ;  $X^3$  is O, S, Se,  $NR^5$  or  $CR^6R^7$ ;  $R^1$  and  $R^2$  are
- 25 each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroarylium,
- 30

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- substituted or unsubstituted heteroaryliumalkyl,  $OR^{10}$ ,  $SR^{10}$ ,  $S(=O)R^{13}$ ,  $S(=O)_2R^{13}$ ,  $NR^{11}R^{12}$  and  $C(=J)R^{13}$ ;  $R^3$  is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylium, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroaryliumalkyl,  $OR^{10}$ ,  $SR^{10}$ ,  $S(=O)R^{13}$ ,  $S(=O)_2R^{13}$ ,  $NR^{11}R^{12}$  and  $C(=J)R^{13}$ ; where
- $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$  and  $R^9$  are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo, pseudohalo,  $OR^{10}$ ,  $NR^{14}R^{15}$  and  $C(=J)R^{13}$ ;
- $R^{10}$ ,  $R^{11}$  and  $R^{12}$  are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl or  $C(=J)R^{13}$ ;
- J is O, S or  $NR^{14}$ ;
- $R^{13}$  is selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted

or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, pseudohalo, OR<sup>16</sup> and NR<sup>14</sup>R<sup>15</sup>;

R<sup>14</sup>, R<sup>15</sup> and R<sup>16</sup> are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl,

**5 heteroaryl, aralkyl and heteroaralkyl;**

where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, heteroarylium, aralkyl, heteroaralkyl and heteroaryliumalkyl moieties of A, D, E, G, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup> and R<sup>13</sup> are unsubstituted or substituted with one or

**10** more substituents, in one embodiment one to three or four substituents, each independently selected from Q<sup>1</sup>, where Q<sup>1</sup> is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl,

**15** cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkylidiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxy carbonyl, aryloxy carbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl,

**20** arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy,

**25** aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-

30 diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-

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- triaryliureido, amidino, alkylamidino, arylamidino, imino, hydroxyimino, alkoxyimino, aryloxyimino, aralkoxyimino, alkylazo, arylazo, aralkylazo, aminothiocabonyl, alkylaminothiocabonyl, arylaminothiocabonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl,
- 5 diarylaminoalkyl, alkylarylaminoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxy carbonylamino, aralkoxy carbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxy carbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxy carbonylamino, alkylsulfonylamino, arylsulfonylamino,
- 10 heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyno, isothiocyano, alkylsulfinyloxy,
- 15 alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxy sulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxy sulfonyl, aminosulfonyl, alkylaminosulfonyl,
- 20 dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two  $Q^1$  groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*,  $-O-(CH_2)_y-O-$ ), thioalkylenoxy (*i.e.*,  $-S-(CH_2)_y-O-$ ) or alkylenedithioxy (*i.e.*,  $-S-(CH_2)_y-S-$ ) where  $y$  is 1 or 2; or two  $Q^1$  groups, which substitute the same atom, together form
- 25 alkylene; and
- each  $Q^1$  is independently unsubstituted or substituted with one or more substituents, in one embodiment one, two or three substituents, each independently selected from  $Q^2$ ;
- each  $Q^2$  is independently halo, pseudohalo, hydroxy, oxo, thia, nitrile,
- 30 nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2

-10-

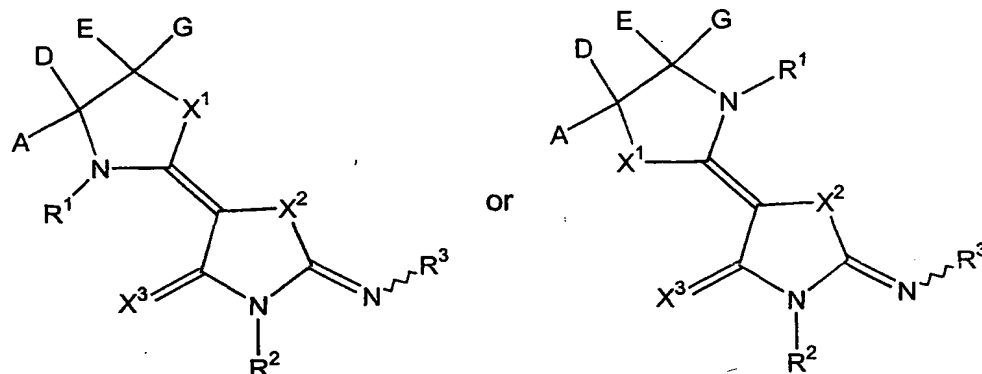
- double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkylidiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl,
- 5 heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxy carbonyl, aryloxy carbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocycloxy, cycloalkoxy,
- 10 perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido,
- 15 N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-trialkylureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl,
- 20 alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl,
- 25 aryloxy carbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxy carbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio,
- 30 perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy,



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- hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylamino sulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl,
- 5 alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylamino sulfonyl or alkylarylaminosulfonyl; or two Q<sup>2</sup> groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*, -O-(CH<sub>2</sub>)<sub>y</sub>-O-), thioalkylenoxy (*i.e.*, -S-(CH<sub>2</sub>)<sub>y</sub>-O-) or alkylenedithioxy (*i.e.*, -S-(CH<sub>2</sub>)<sub>y</sub>-S-) where y is 1 or 2; or two Q<sup>2</sup> groups, which substitute the same
- 10 atom, together form alkylene;
- each Q<sup>2</sup> is independently unsubstituted or substituted with one or more, in one embodiment one, two or three, substituents each independently selected from alkyl, halo and pseudohalo;
- R<sup>50</sup> is hydroxy, alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or
- 15 -NR<sup>70</sup>R<sup>71</sup>, where R<sup>70</sup> and R<sup>71</sup> are each independently hydrogen, alkyl, aralkyl, aryl, heteroaryl, heteroaralkyl or heterocyclyl, or R<sup>70</sup> and R<sup>71</sup> together form alkylene, azaalkylene, oxaalkylene or thiaalkylene;
- R<sup>51</sup>, R<sup>52</sup> and R<sup>53</sup> are each independently hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl;
- 20 R<sup>60</sup> is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl; and
- R<sup>63</sup> is alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or -NR<sup>70</sup>R<sup>71</sup>.
- In another embodiment, the compounds for use in the compositions and methods provided herein have formulae I:

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or a pharmaceutically acceptable derivative thereof, where A, D, E and G are selected from (i) or (ii) as follows:

- (i) A and G are each independently selected from hydrogen,  
 5 substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl,  
 substituted or unsubstituted alkynyl, substituted or unsubstituted  
 cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or  
 unsubstituted cycloalkylalkyl, substituted or unsubstituted  
 heterocyclalkyl, substituted or unsubstituted aryl, substituted or  
 10 unsubstituted heteroaryl, substituted or unsubstituted aralkyl,  
 substituted or unsubstituted heteroaralkyl, substituted or unsubstituted  
 heteroarylium, substituted or unsubstituted heteroaryliumalkyl, halo,  
 pseudohalo, OR<sup>10</sup>, SR<sup>10</sup>, S(=O)R<sup>13</sup>, S(=O)<sub>2</sub>R<sup>13</sup>, NR<sup>11</sup>R<sup>12</sup> and C(=J)R<sup>13</sup>,  
 or A and G together form substituted or unsubstituted alkylene,  
 15 substituted or unsubstituted azaalkylene, substituted or unsubstituted  
 oxaalkylene, substituted or unsubstituted thiaalkylene, substituted or  
 unsubstituted alkenylene, substituted or unsubstituted alkynylene,  
 substituted or unsubstituted 1,3-butadienylene, substituted or  
 unsubstituted 1-aza-1,3-butadienylene, or substituted or unsubstituted  
 20 2-aza-1,3-butadienylene;

D and E are each independently selected from hydrogen,  
 substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl,  
 substituted or unsubstituted alkynyl, substituted or unsubstituted  
 cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or

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- unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo and pseudohalo or D and E together form a bond; or
- (ii) A and D; or E and G; together form substituted or unsubstituted alkylene, substituted or unsubstituted azaalkylene, substituted or unsubstituted oxaalkylene, or substituted or unsubstituted thiaalkylene; and the others of A, D, E and G are selected as in (i);
- $X^1$  and  $X^2$  are each independently selected from O, S,  $S(=O)$ ,  $S(=O)_2$ , Se,  $NR^5$ ,  $CR^6R^7$  and  $CR^8=CR^9$ ;  $X^3$  is O, S, Se,  $NR^5$  or  $CR^6R^7$ ;  $R^1$  and  $R^2$  are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroarylium, substituted or unsubstituted heteroaryliumalkyl,  $OR^{10}$ ,  $SR^{10}$ ,  $S(=O)R^{13}$ ,  $S(=O)_2R^{13}$ ,  $NR^{11}R^{12}$  and  $C(=J)R^{13}$ ;  $R^3$  is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylium, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroaryliumalkyl,  $OR^{10}$ ,  $SR^{10}$ ,  $S(=O)R^{13}$ ,  $S(=O)_2R^{13}$ ,  $NR^{11}R^{12}$  and  $C(=J)R^{13}$ ; where  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$  and  $R^9$  are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl,

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- substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo, pseudohalo, OR<sup>10</sup>, NR<sup>14</sup>R<sup>15</sup> and C(=J)R<sup>13</sup>;
- 5 R<sup>10</sup>, R<sup>11</sup> and R<sup>12</sup> are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl,
- 10 substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl or C(=J)R<sup>13</sup>;
- J is O, S or NR<sup>14</sup>;
- R<sup>13</sup> is selected from hydrogen, substituted or unsubstituted alkyl,
- 15 substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, pseudohalo, OR<sup>16</sup> and NR<sup>14</sup>R<sup>15</sup>;
- 20 R<sup>14</sup>, R<sup>15</sup> and R<sup>16</sup> are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl;
- where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, heteroarylium, aralkyl, heteroaralkyl and heteroaryliumalkyl moieties of A, D, E, G, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup> and R<sup>13</sup> are unsubstituted or substituted with one or more substituents, in one embodiment one to three or four substituents, each independently selected from Q<sup>1</sup>, where Q<sup>1</sup> is halo, pseudohalo, hydroxy, oxo,
- 25 thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to

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- 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl,
- 5 heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocycloxy, cycloalkoxy,
- 10 perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido,
- 15 N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl,
- 20 alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl,
- 25 aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio,
- 30 perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy,

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- hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl,
- 5 alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two Q<sup>1</sup> groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*, -O-(CH<sub>2</sub>)<sub>y</sub>-O-), thioalkylenoxy (*i.e.*, -S-(CH<sub>2</sub>)<sub>y</sub>-O-) or alkylenedithioxy (*i.e.*, -S-(CH<sub>2</sub>)<sub>y</sub>-S-) where y is 1 or 2; or two Q<sup>1</sup> groups, which substitute the same
- 10 atom, together form alkylene; and
- each Q<sup>1</sup> is independently unsubstituted or substituted with one or more substituents, in one embodiment one, two or three substituents, each independently selected from Q<sup>2</sup>;
- each Q<sup>2</sup> is independently halo, pseudohalo, hydroxy, oxo, thia, nitrile,
- 15 nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkylidiarylsilyl,
- 20 triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxy carbonyl, aryloxy carbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy,
- 25 aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy,
- 30 guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido,

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- N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl,
- 5 alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminominoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylaminomino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl,
- 10 aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclisulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio,
- 15 perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyno, isothiocyno, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl,
- 20 arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two  $Q^2$  groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*,  $-O-(CH_2)_y-O-$ ), thioalkylenoxy (*i.e.*,  $-S-(CH_2)_y-O-$ ) or alkylenedithioxy (*i.e.*,  $-S-(CH_2)_y-S-$ ) where y is 1 or 2; or two  $Q^2$  groups, which substitute the same atom, together form alkylene;
- 25  $R^{50}$  is hydroxy, alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or  $-NR^{70}R^{71}$ , where  $R^{70}$  and  $R^{71}$  are each independently hydrogen, alkyl, aralkyl, aryl, heteroaryl, heteroaralkyl or heterocyclyl, or  $R^{70}$  and  $R^{71}$  together form
- 30 alkylene, azaalkylene, oxaalkylene or thiaalkylene;

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$R^{51}$ ,  $R^{52}$  and  $R^{53}$  are each independently hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclalkyl;

$R^{60}$  is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclalkyl; and

5  $R^{63}$  is alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or  $-NR^{70}R^{71}$ .

In certain embodiments herein, the compounds are selected with the proviso that when  $R^3$  is substituted or unsubstituted heteroarylium then the heteroatom substituent is not alkyl or aryl. In another embodiment, the compounds are selected with the proviso that  $R^3$  is not substituted or

10 unsubstituted heteroarylium or substituted or unsubstituted heteroaryliumalkyl. In other embodiments, the compounds are selected with the proviso that  $R^3$  is not heteroaryl. In further embodiments, the compounds are selected with the proviso that  $R^3$  is not alkyl. In another embodiment, the compounds are selected with the proviso that  $R^3$  is not heterocycloaryl (*i.e.*, an aryl group  
15 possessing a fused heterocyclic moiety).

The groups A, D, E, G,  $X^1$ ,  $X^2$ ,  $X^3$ ,  $R^1$ ,  $R^2$  and  $R^3$  are selected such that the resulting compound has nuclear receptor modulation activity, such as in at least one assay described herein, such as FXR antagonist or agonist activity, and, in certain embodiments, at an  $IC_{50}$  or  $EC_{50}$  of less than about 100  $\mu M$ .

20 The FXR  $IC_{50}$  or  $EC_{50}$  values for the compounds provided herein are, in certain embodiments, less than about 50  $\mu M$ , 25  $\mu M$ , 10  $\mu M$ , 1  $\mu M$ , 100 nM, 10 nM or 1 nM.

Also of interest are any pharmaceutically-acceptable derivatives, including salts, esters, enol ethers, enol esters, solvates, hydrates and

25 prodrugs of the compounds described herein. Pharmaceutically-acceptable salts, include, but are not limited to, amine salts, such as but not limited to N,N'-dibenzylethylenediamine, chlorprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-para-chlorobenzyl-2-pyrrolidin-1'-ylmethylbenzimidazole, diethylamine and other alkylamines,  
30 piperazine and tris(hydroxymethyl)aminomethane; alkali metal salts, such as



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- but not limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but not limited to zinc, aluminum, and other metal salts, such as but not limited to sodium hydrogen phosphate and disodium phosphate; and also
- 5 including, but not limited to, salts of mineral acids, such as but not limited to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates and fumarates.

- Pharmaceutical compositions formulated for administration by an
- 10 appropriate route and means containing effective concentrations of one or more of the compounds provided herein, or pharmaceutically acceptable derivatives thereof, that deliver amounts effective for the treatment, prevention, or amelioration of one or more symptoms of diseases or disorders that are modulated or otherwise affected by nuclear receptor activity, including
- 15 FXR, LXR and/or orphan nuclear receptor activity, or in which nuclear receptor activity, including FXR, LXR and/or orphan nuclear receptor activity, is implicated, are also provided. The effective amounts and concentrations are effective for ameliorating any of the symptoms of any of the diseases or disorders.
- 20 Methods for treatment, prevention, or amelioration of one or more symptoms of diseases or disorders mediated by or in which nuclear receptor activity, including FXR, LXR and/or orphan nuclear receptor activity, is implicated, are provided. Such methods include methods of treatment, prevention and amelioration of one or more symptoms of
- 25 hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by
- 30 a perturbed epidermal barrier function, hyperlipidemia, cholestasis, peripheral occlusive disease, ischemic stroke, conditions of disturbed differentiation or

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excess proliferation of the epidermis or mucous membrane, or cardiovascular disorders, using one or more of the compounds provided herein, or pharmaceutically acceptable derivatives thereof.

- Methods of modulating the activity of nuclear receptors, including FXR, LXR and/or orphan nuclear receptors, using the compounds and compositions provided herein are also provided. The compounds and compositions provided herein are active in assays that measure the activity of nuclear receptors, including FXR, LXR and/or orphan nuclear receptors, including the assays provided herein. These methods include inhibiting and up-regulating the activity of nuclear receptors, including FXR, LXR and/or orphan nuclear receptors.

Methods of reducing cholesterol levels in a subject in need thereof by administration of one or more compounds or compositions provided herein are also provided.

- Methods of modulating cholesterol metabolism using the compounds and compositions provided herein are provided.

- Methods of treating, preventing, or ameliorating one or more symptoms of diseases or disorders which are affected by cholesterol, triglyceride, or bile acid levels by administration of one or more of the compounds and compositions provided herein are also provided.

- In practicing the methods, effective amounts of the compounds or compositions containing therapeutically effective concentrations of the compounds, which are formulated for systemic delivery, including parenteral, oral, or intravenous delivery, or for local or topical application, for the treatment of nuclear receptor, including FXR, LXR and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including FXR, LXR and/or orphan nuclear receptor activity, is implicated, including, but not limited to, hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer,

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Alzheimer's diseases, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, hyperlipidemia, cholestasis, peripheral occlusive disease, ischemic stroke, conditions of disturbed differentiation or excess proliferation of the epidermis

5 or mucous membrane, or cardiovascular disorders, are administered to an individual exhibiting the symptoms of these diseases or disorders. The amounts are effective to ameliorate or eliminate one or more symptoms of the diseases or disorders.

Articles of manufacture containing packaging material, a compound or

10 composition, or pharmaceutically acceptable derivative thereof, provided herein, which is effective for modulating the activity of nuclear receptors, including FXR, LXR and/or orphan nuclear receptors, or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor, including FXR, LXR and/or orphan nuclear receptor, mediated diseases or

15 disorders, or diseases or disorders in which nuclear receptor activity, including FXR, LXR and/or orphan nuclear receptor activity, is implicated, within the packaging material, and a label that indicates that the compound or composition, or pharmaceutically acceptable derivative thereof, is used for modulating the activity of nuclear receptors, including FXR, LXR and/or

20 orphan nuclear receptors, or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor, including FXR, LXR and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including FXR, LXR and/or orphan nuclear receptor activity, is implicated, are provided.

## 25 BRIEF DESCRIPTION OF DRAWINGS

Figure 1 provides *in vitro* data for the compounds whose synthesis is described in the Examples. Average EC<sub>50</sub> ("EC50\_AVG") for FXR agonism is provided as follows: A = 0.0001-0.01  $\mu$ M, B = 0.01-0.1  $\mu$ M, C = 0.1-1.0  $\mu$ M, D = 1.0-10.0  $\mu$ M and NC = not calculated or inactive. Average percent efficacy

30 ("EFF\_AVG") for FXR agonism relative to control (chenodeoxycholic acid, CDCA) is provided as follows: A = >150%, B = 100-150%, C = 50-100%, D =

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- 0-50% and NC = not calculated or inactive. Average  $IC_{50}$  ("IC50\_AVG") for FXR antagonism is provided as follows: A = 0.0001-0.01  $\mu$ M, B = 0.01-0.1  $\mu$ M, C = 0.1-1.0  $\mu$ M and D = 1.0-10.0  $\mu$ M. Average percent inhibition ("INHIB\_AVG") for FXR antagonism relative to control (chenodeoxycholic acid, CDCA) is provided as follows: E = >75%, F = 50-75%, G = 25-50%, H = 0-25% and NEG = negative.

## DETAILED DESCRIPTION OF EMBODIMENTS

### A. Definitions

- Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.
- As used herein, a nuclear receptor is a member of a superfamily of regulatory proteins that are receptors for, e.g., steroids, retinoids, vitamin D and thyroid hormones. These proteins bind to cis-acting elements in the promoters of their target genes and modulate gene expression in response to a ligand therefor. Nuclear receptors may be classified based on their DNA binding properties. For example, the glucocorticoid, estrogen, androgen, progestin and mineralocorticoid receptors bind as homodimers to hormone response elements (HREs) organized as inverted repeats. Another example are receptors, including those activated by retinoic acid, thyroid hormone, vitamin D<sub>3</sub>, fatty acids/peroxisome proliferators and ecdysone, that bind to HREs as heterodimers with a common partner, the retinoid X receptor (RXR). Among the latter receptors are FXR and LXR.

As used herein, an orphan nuclear receptor is a nuclear receptor for which the natural ligand is unknown.

- As used herein, the term farnesoid X receptor or FXR refers to all mammalian forms of such receptor including, for example, alternative splice isoforms and naturally occurring isoforms. Representative FXR species

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include, without limitation rat FXR (SEQ ID NO. 5), mouse FXR, and human FXR (SEQ ID NO. 7).

As used herein, liver X receptor or LXR or UR refers to a nuclear receptor implicated in cholesterol homeostasis. As used herein, the term LXR  
5 refers to both LXR $\alpha$  and LXR $\beta$ , two forms of the protein found in mammals. Liver X receptor- $\alpha$  or LXR $\alpha$  refers to the receptor described in U.S. Patent No. 5,757,661 and Willy *et al.* (1995) *Gene Dev.* 9(9):1033-1045. Liver X receptor- $\beta$  or LXR $\beta$  refers to the receptor described in Peet *et al.* (1998) *Curr. Opin. Genet. Dev.* 8(5):571-575; Song *et al.* (1995) *Ann. N.Y. Acad. Sci.* 761:38-49; Alberti *et al.* (2000) *Gene* 243(1-2):93-103; and references cited  
10 therein.

As used herein, pharmaceutically acceptable derivatives of a compound include salts, esters, enol ethers, enol esters, acetals, ketals, orthoesters, hemiacetals, hemiketals, acids, bases, solvates, hydrates or  
15 prodrugs thereof. Such derivatives may be readily prepared by those of skill in this art using known methods for such derivatization. The compounds produced may be administered to animals or humans without substantial toxic effects and either are pharmaceutically active or are prodrugs. Pharmaceutically acceptable salts include, but are not limited to, amine salts,  
20 such as but not limited to N,N'-dibenzylethylenediamine, chloroprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-para-chlorobenzyl-2-pyrrolidin-1'-ylmethylbenzimidazole, diethylamine and other alkylamines, piperazine and tris(hydroxymethyl)aminomethane; alkali  
25 metal salts, such as but not limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but not limited to zinc; and other metal salts, such as but not limited to sodium hydrogen phosphate and disodium phosphate; and also including, but not limited to, salts of mineral acids, such  
30 as but not limited to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates,

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- ascorbates, succinates, butyrates, valerates and fumarates. Pharmaceutically acceptable esters include, but are not limited to, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl and heterocyclyl esters of acidic groups, including, but not limited to, carboxylic acids, phosphoric acids, phosphinic acids, sulfonic acids, sulfinic acids and boronic acids.
- 5 Pharmaceutically acceptable enol ethers include, but are not limited to, derivatives of formula  $C=C(OR)$  where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl or heterocyclyl.
- Pharmaceutically acceptable enol esters include, but are not limited to, derivatives of formula  $C=C(OC(O)R)$  where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl or heterocyclyl.
- 10 Pharmaceutically acceptable solvates and hydrates are complexes of a compound with one or more solvent or water molecules, or 1 to about 100, or 1 to about 10, or one to about 2, 3 or 4, solvent or water molecules.
- 15 As used herein, treatment means any manner in which one or more of the symptoms of a disease or disorder are ameliorated or otherwise beneficially altered. Treatment also encompasses any pharmaceutical use of the compositions herein, such as use for treating a nuclear receptor, including FXR, LXR and/or orphan nuclear receptor, mediated diseases or disorders, or
- 20 diseases or disorders in which nuclear receptor activity, including FXR, LXR and/or orphan nuclear receptor activity, is implicated.
- As used herein, amelioration of the symptoms of a particular disorder by administration of a particular compound or pharmaceutical composition refers to any lessening, whether permanent or temporary, lasting or transient
- 25 that can be attributed to or associated with administration of the composition.
- As used herein, the  $IC_{50}$  refers to an amount, concentration or dosage of a particular test compound that achieves a 50% inhibition of a maximal response, such as modulation of FXR activity, in an assay that measures such response.
- 30 As used herein,  $EC_{50}$  refers to a dosage, concentration or amount of a particular test compound that elicits a dose-dependent response at 50% of

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maximal expression of a particular response that is induced, provoked or potentiated by the particular test compound.

As used herein, a prodrug is a compound that, upon *in vivo* administration, is metabolized by one or more steps or processes or otherwise converted to the biologically, pharmaceutically or therapeutically active form of the compound. To produce a prodrug, the pharmaceutically active compound is modified such that the active compound will be regenerated by metabolic processes. The prodrug may be designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug or to alter other characteristics or properties of a drug. By virtue of knowledge of pharmacodynamic processes and drug metabolism *in vivo*, those of skill in this art, once a pharmaceutically active compound is known, can design prodrugs of the compound (see, e.g., Nogrady (1985) *Medicinal Chemistry A Biochemical Approach*, Oxford University Press, New York, pages 388-392).

It is to be understood that the compounds provided herein may contain chiral centers. Such chiral centers may be of either the (R) or (S) configuration, or may be a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure, or be stereoisomeric or diastereomeric mixtures. In the case of amino acid residues, such residues may be of either the L- or D-form. The configuration for naturally occurring amino acid residues is generally L. When not specified the residue is the L form. As used herein, the term "amino acid" refers to  $\alpha$ -amino acids which are racemic, or of either the D- or L-configuration. The designation "d" preceding an amino acid designation (e.g., dAla, dSer, dVal, etc.) refers to the D-isomer of the amino acid. The designation "dl" preceding an amino acid designation (e.g., dlPip) refers to a mixture of the L- and D-isomers of the amino acid. It is to be understood that the chiral centers of the compounds provided herein may undergo epimerization *in vivo*. As such, one of skill in the art will recognize that administration of a compound in its (R) form is equivalent, for compounds

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that undergo epimerization *in vivo*, to administration of the compound in its (S) form.

As used herein, substantially pure means sufficiently homogeneous to appear free of readily detectable impurities as determined by standard  
5 methods of analysis, such as thin layer chromatography (TLC), gel electrophoresis, high performance liquid chromatography (HPLC) and mass spectrometry (MS), used by those of skill in the art to assess such purity, or sufficiently pure such that further purification would not detectably alter the physical and chemical properties, such as enzymatic and biological activities,  
10 of the substance. Methods for purification of the compounds to produce substantially chemically pure compounds are known to those of skill in the art. A substantially chemically pure compound may, however, be a mixture of stereoisomers. In such instances, further purification might increase the specific activity of the compound. The instant disclosure is meant to include  
15 all such possible isomers, as well as, their racemic and optically pure forms. Optically active (+) and (-), (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, such as reverse phase HPLC. When the compounds described herein contain olefinic double bonds or other centers of geometric  
20 asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

As used herein, the nomenclature alkyl, alkoxy, carbonyl, etc. is used as is generally understood by those of skill in this art.

25 As used herein, alkyl, alkenyl and alkynyl carbon chains, if not specified, contain from 1 to 20 carbons, or 1 to 16 carbons, and are straight or branched. Alkenyl carbon chains of from 2 to 20 carbons, in certain embodiments, contain 1 to 8 double bonds, and the alkenyl carbon chains of 2 to 16 carbons, in certain embodiments, contain 1 to 5 double bonds. Alkynyl  
30 carbon chains of from 2 to 20 carbons, in certain embodiments, contain 1 to 8 triple bonds, and the alkynyl carbon chains of 2 to 16 carbons, in certain



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embodiments, contain 1 to 5 triple bonds. Exemplary alkyl, alkenyl and alkynyl groups herein include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl, n-butyl, sec-butyl, tert-butyl, isopentyl, neopentyl, tert-pentylyl and isohexyl. As used herein, lower alkyl, lower alkenyl, and lower alkynyl refer to carbon chains having from about 1 or about 2 carbons up to about 6 carbons. As used herein, "alk(en)(yn)yl" refers to an alkyl group containing at least one double bond and at least one triple bond.

As used herein, "cycloalkyl" refers to a saturated mono- or multicyclic ring system, in certain embodiments of 3 to 10 carbon atoms, in other embodiments of 3 to 6 carbon atoms; cycloalkenyl and cycloalkynyl refer to mono- or multicyclic ring systems that respectively include at least one double bond and at least one triple bond. Cycloalkenyl and cycloalkynyl groups may, in certain embodiments, contain 3 to 10 carbon atoms, with cycloalkenyl groups, in further embodiments, containing 4 to 7 carbon atoms and cycloalkynyl groups, in further embodiments, containing 8 to 10 carbon atoms. The ring systems of the cycloalkyl, cycloalkenyl and cycloalkynyl groups may be composed of one ring or two or more rings which may be joined together in a fused, bridged or spiro-connected fashion. "Cycloalk(en)(yn)yl" refers to a cycloalkyl group containing at least one double bond and at least one triple bond.

As used herein, "substituted alkyl," "substituted alkenyl," "substituted alkynyl," "substituted cycloalkyl," "substituted cycloalkenyl," and "substituted cycloalkynyl" refer to alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl and cycloalkynyl groups, respectively, that are substituted with one or more substituents, in certain embodiments one to three or four substituents, where the substituents are as defined herein, generally selected from Q<sup>1</sup>.

As used herein, "aryl" refers to aromatic monocyclic or multicyclic groups containing from 6 to 19 carbon atoms. Aryl groups include, but are not limited to groups such as fluorenyl, substituted fluorenyl, phenyl, substituted phenyl, naphthyl and substituted naphthyl.

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As used herein, "heteroaryl" refers to a monocyclic or multicyclic aromatic ring system, in certain embodiments, of about 5 to about 15 members where one or more, in one embodiment 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including  
5 but not limited to, nitrogen, oxygen or sulfur. The heteroaryl group may be optionally fused to a benzene ring. Heteroaryl groups include, but are not limited to, furyl, imidazolyl, pyrrolidinyl, pyrimidinyl, tetrazolyl, thienyl, pyridyl, pyrrolyl, N-methylpyrrolyl, quinolinyl and isoquinolinyl.

As used herein, a "heteroarylium" group is a heteroaryl group that is  
10 positively charged on one or more of the heteroatoms.

As used herein, "heterocyclyl" refers to a monocyclic or multicyclic non-aromatic ring system, in one embodiment of 3 to 10 members, in another embodiment of 4 to 7 members, in a further embodiment of 5 to 6 members, where one or more, in certain embodiments, 1 to 3, of the atoms in the ring  
15 system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur. In embodiments where the heteroatom(s) is(are) nitrogen, the nitrogen is optionally substituted with alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, acyl, guanidino, or the nitrogen may be  
20 quaternized to form an ammonium group where the substituents are selected as above.

As used herein, "substituted aryl," "substituted heteroaryl" and "substituted heterocyclyl" refer to aryl, heteroaryl and heterocyclyl groups, respectively, that are substituted with one or more substituents, in certain  
25 embodiments one to three or four substituents, where the substituents are as defined herein, generally selected from Q<sup>1</sup>.

As used herein, "aralkyl" refers to an alkyl group in which one of the hydrogen atoms of the alkyl is replaced by an aryl group.

As used herein, "heteroaralkyl" refers to an alkyl group in which one of  
30 the hydrogen atoms of the alkyl is replaced by a heteroaryl group.

As used herein, "halo", "halogen" or "halide" refers to F, Cl, Br or I.

As used herein, pseudohalides or pseudohalo groups are groups that behave substantially similar to halides. Such compounds can be used in the same manner and treated in the same manner as halides. Pseudohalides include, but are not limited to, cyanide, cyanate, thiocyanate, selenocyanate, 5 trifluoromethoxy, and azide.

As used herein, "haloalkyl" refers to an alkyl group in which one or more of the hydrogen atoms are replaced by halogen. Such groups include, but are not limited to, chloromethyl, trifluoromethyl and 1-chloro-2-fluoroethyl.

As used herein, "haloalkoxy" refers to RO- in which R is a haloalkyl 10 group.

As used herein, "sulfinyl" or "thionyl" refers to -S(O)-. As used herein, "sulfonyl" or "sulfuryl" refers to -S(O)<sub>2</sub>-. As used herein, "sulfo" refers to -S(O)<sub>2</sub>O-.

As used herein, "carboxy" refers to a divalent radical, -C(O)O-.

15 As used herein, "aminocarbonyl" refers to -C(O)NH<sub>2</sub>.

As used herein, "alkylaminocarbonyl" refers to -C(O)NHR in which R is alkyl, including lower alkyl. As used herein, "dialkylaminocarbonyl" refers to -C(O)NR'R in which R' and R are independently alkyl, including lower alkyl; "carboxamide" refers to groups of formula -NR'COR in which R' and R are 20 independently alkyl, including lower alkyl.

As used herein, "diarylaminocarbonyl" refers to -C(O)NRR' in which R and R' are independently selected from aryl, including lower aryl, such as phenyl.

As used herein, "arylalkylaminocarbonyl" refers to -C(O)NRR' in which 25 one of R and R' is aryl, including lower aryl, such as phenyl, and the other of R and R' is alkyl, including lower alkyl.

As used herein, "arylaminocarbonyl" refers to -C(O)NHR in which R is aryl, including lower aryl, such as phenyl.

As used herein, "hydroxycarbonyl" refers to -COOH.

30 As used herein, "alkoxycarbonyl" refers to -C(O)OR in which R is alkyl, including lower alkyl.

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As used herein, "aryloxycarbonyl" refers to  $-C(O)OR$  in which R is aryl, including lower aryl, such as phenyl.

As used herein, "alkoxy" and "alkylthio" refer to  $RO-$  and  $RS-$ , in which R is alkyl, including lower alkyl.

- 5 As used herein, "aryloxy" and "arylthio" refer to  $RO-$  and  $RS-$ , in which R is aryl, including lower aryl, such as phenyl.

- As used herein, "alkylene" refers to a straight, branched or cyclic, in certain embodiments straight or branched, divalent aliphatic hydrocarbon group, in one embodiment having from 1 to about 20 carbon atoms, in another
- 10 embodiment having from 1 to 12 carbons. In a further embodiment alkylene includes lower alkylene. There may be optionally inserted along the alkylene group one or more oxygen, sulfur, including  $S(=O)$  and  $S(=O)_2$  groups, or substituted or unsubstituted nitrogen atoms, including  $-NR-$  and  $-N^+RR-$  groups, where the nitrogen substituent(s) is(are) alkyl, aryl, aralkyl, heteroaryl,
- 15 heteroaralkyl or  $COR'$ , where  $R'$  is alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl,  $-OY$  or  $-NYY$ , where Y is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl. Alkylene groups include, but are not limited to, methylene ( $-CH_2-$ ), ethylene ( $-CH_2CH_2-$ ), propylene ( $-(CH_2)_3-$ ), methylenedioxy ( $-O-CH_2-O-$ ) and ethylenedioxy ( $-O-(CH_2)_2-O-$ ). The term "lower alkylene" refers to alkylene
- 20 groups having 1 to 6 carbons. In certain embodiments, alkylene groups are lower alkylene, including alkylene of 1 to 3 carbon atoms.

- As used herein, "azaalkylene" refers to  $-(CRR)_n-NR-(CRR)_m-$ , where n and m are each independently an integer from 0 to 4. As used herein, "oxaalkylene" refers to  $-(CRR)_n-O-(CRR)_m-$ , where n and m are each
- 25 independently an integer from 0 to 4. As used herein, "thiaalkylene" refers to  $-(CRR)_n-S-(CRR)_m-$ ,  $-(CRR)_n-S(=O)-(CRR)_m-$ , and  $-(CRR)_n-S(=O)_2-(CRR)_m-$ , where n and m are each independently an integer from 0 to 4. In certain embodiments herein, the "R" groups in the definitions of azaalkylene, oxaalkylene and thiaalkylene are each independently selected from hydrogen
- 30 and  $Q^1$ , as defined herein.

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As used herein, "alkenylene" refers to a straight, branched or cyclic, in one embodiment straight or branched, divalent aliphatic hydrocarbon group, in certain embodiments having from 2 to about 20 carbon atoms and at least one double bond, in other embodiments 1 to 12 carbons. In further

- 5   embodiments, alkenylene groups include lower alkenylene. There may be optionally inserted along the alkenylene group one or more oxygen, sulfur or substituted or unsubstituted nitrogen atoms, where the nitrogen substituent is alkyl. Alkenylene groups include, but are not limited to,  $\text{—CH=CH—}$ ,  $\text{CH=CH—}$  and  $\text{—CH=CH-CH}_2\text{—}$ . The term "lower alkenylene" refers to
- 10   alkenylene groups having 2 to 6 carbons. In certain embodiments, alkenylene groups are lower alkenylene, including alkenylene of 3 to 4 carbon atoms.

As used herein, "alkynylene" refers to a straight, branched or cyclic, in certain embodiments straight or branched, divalent aliphatic hydrocarbon group, in one embodiment having from 2 to about 20 carbon atoms and at

- 15   least one triple bond, in another embodiment 1 to 12 carbons. In a further embodiment, alkynylene includes lower alkynylene. There may be optionally inserted along the alkynylene group one or more oxygen, sulfur or substituted or unsubstituted nitrogen atoms, where the nitrogen substituent is alkyl. Alkynylene groups include, but are not limited to,  $\text{—C}\equiv\text{C—C}\equiv\text{C—}$ ,  $\text{—C}\equiv\text{C—}$  and  $\text{—C}\equiv\text{C-CH}_2\text{—}$ . The term "lower alkynylene" refers to alkynylene groups having 2
- 20   to 6 carbons. In certain embodiments, alkynylene groups are lower alkynylene, including alkynylene of 3 to 4 carbon atoms.

As used herein, "alk(en)(yn)ylene" refers to a straight, branched or cyclic, in certain embodiments straight or branched, divalent aliphatic

- 25   hydrocarbon group, in one embodiment having from 2 to about 20 carbon atoms and at least one triple bond, and at least one double bond; in another embodiment 1 to 12 carbons. In further embodiments, alk(en)(yn)ylene includes lower alk(en)(yn)ylene. There may be optionally inserted along the alkynylene group one or more oxygen, sulfur or substituted or unsubstituted
- 30   nitrogen atoms, where the nitrogen substituent is alkyl. Alk(en)(yn)ylene groups include, but are not limited to,  $\text{—C=C—(CH}_2\text{)}_n\text{—C}\equiv\text{C—}$ , where n is 1 or

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2. The term "lower alk(en)(yn)ylene" refers to alk(en)(yn)ylene groups having up to 6 carbons. In certain embodiments, alk(en)(yn)ylene groups have about 4 carbon atoms.

As used herein, "cycloalkylene" refers to a divalent saturated mono- or multicyclic ring system, in certain embodiments of 3 to 10 carbon atoms, in other embodiments 3 to 6 carbon atoms; cycloalkenylene and cycloalkynylene refer to divalent mono- or multicyclic ring systems that respectively include at least one double bond and at least one triple bond. Cycloalkenylene and cycloalkynylene groups may, in certain embodiments, contain 3 to 10 carbon atoms, with cycloalkenylene groups in certain embodiments containing 4 to 7 carbon atoms and cycloalkynylene groups in certain embodiments containing 8 to 10 carbon atoms. The ring systems of the cycloalkylene, cycloalkenylene and cycloalkynylene groups may be composed of one ring or two or more rings which may be joined together in a fused, bridged or spiro-connected fashion. "Cycloalk(en)(yn)ylene" refers to a cycloalkylene group containing at least one double bond and at least one triple bond.

As used herein, "substituted alkylene," "substituted alkenylene," "substituted alkynylene," "substituted cycloalkylene," "substituted cycloalkenylene," and "substituted cycloalkynylene" refer to alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene and cycloalkynylene groups, respectively, that are substituted with one or more substituents, in certain embodiments one to three or four substituents, where the substituents are as defined herein, generally selected from Q<sup>1</sup>.

As used herein, "arylene" refers to a monocyclic or polycyclic, in certain embodiments monocyclic, divalent aromatic group, in one embodiment having from 5 to about 20 carbon atoms and at least one aromatic ring, in another embodiment 5 to 12 carbons. In further embodiments, arylene includes lower arylene. Arylene groups include, but are not limited to, 1,2-, 1,3- and 1,4-phenylene. The term "lower arylene" refers to arylene groups having 5 or 6 carbons.

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As used herein, "heteroarylene" refers to a divalent monocyclic or multicyclic aromatic ring system, in one embodiment of about 5 to about 15 members where one or more, in certain embodiments 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur.

As used herein, "heterocyclylene" refers to a divalent monocyclic or multicyclic non-aromatic ring system, in certain embodiments of 3 to 10 members, in one embodiment 4 to 7 members, in another embodiment 5 to 6 members, where one or more, including 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur.

As used herein, "substituted arylene," "substituted heteroarylene" and "substituted heterocyclylene" refer to arylene, heteroarylene and heterocyclylene groups, respectively, that are substituted with one or more substituents, in certain embodiments one to three of four substituents, where the substituents are as defined herein, generally selected from Q<sup>1</sup>.

As used herein, "alkylidene" refers to a divalent group, such as =CR'R", which is attached to one atom of another group, forming a double bond. Alkylidene groups include, but are not limited to, methyldene (=CH<sub>2</sub>) and ethyldene (=CHCH<sub>3</sub>). As used herein, "arylalkylidene" refers to an alkylidene group in which either R' or R" is an aryl group. "Cycloalkylidene" groups are those where R' and R" are linked to form a carbocyclic ring.

"Heterocyclylidene" groups are those where at least one of R' and R" contain a heteroatom in the chain, and R' and R" are linked to form a heterocyclic ring.

As used herein, "amido" refers to the divalent group -C(O)NH-. "Thioamido" refers to the divalent group -C(S)NH-. "Oxyamido" refers to the divalent group -OC(O)NH-. "Thiaamido" refers to the divalent group -SC(O)NH-. "Dithiaamido" refers to the divalent group -SC(S)NH-. "Ureido" refers to the divalent group -HNC(O)NH-. "Thioureido" refers to the divalent group -HNC(S)NH-.

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As used herein, "semicarbazide" refers to  $\text{-NHC(O)NHNH-}$ .

"Carbazate" refers to the divalent group  $\text{-OC(O)NHNH-}$ . "Isothiocarbazate"

refers to the divalent group  $\text{-SC(O)NHNH-}$ . "Thiocarbazate" refers to the

divalent group  $\text{-OC(S)NHNH-}$ . "Sulfonylhydrazide" refers to the group -

- 5  $\text{SO}_2\text{NHNH-}$ . "Hydrazide" refers to the divalent group  $\text{-C(O)NHNH-}$ . "Azo" refers to the divalent group  $\text{-N=N-}$ . "Hydrazinyl" refers to the divalent group  $\text{-NH-NH-}$ .

Where the number of any given substituent is not specified (e.g.,

"haloalkyl"), there may be one or more substituents present. For example,

- 10 "haloalkyl" may include one or more of the same or different halogens. As another example, " $\text{C}_{1-3}$ alkoxyphenyl" may include one or more of the same or different alkoxy groups containing one, two or three carbons.

As used herein, the following terms have their accepted meaning in the chemical literature:

15	AcOH	acetic acid
	$\text{CHCl}_3$	chloroform
	conc	concentrated
	DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
20	DCM	dichloromethane
	DME	1,2-dimethoxyethane
	DMF	<i>N,N</i> -dimethylformamide
	DMSO	dimethylsulfoxide
25	EtOAc	ethyl acetate
	EtOH	ethanol (100%)
	$\text{Et}_2\text{O}$	diethyl ether
	Hex	hexanes
30	$\text{H}_2\text{SO}_4$	sulfuric acid
	MeCN	acetonitrile
	MeOH	methanol
	Pd/C	palladium on activated carbon
	TEA	triethylamine



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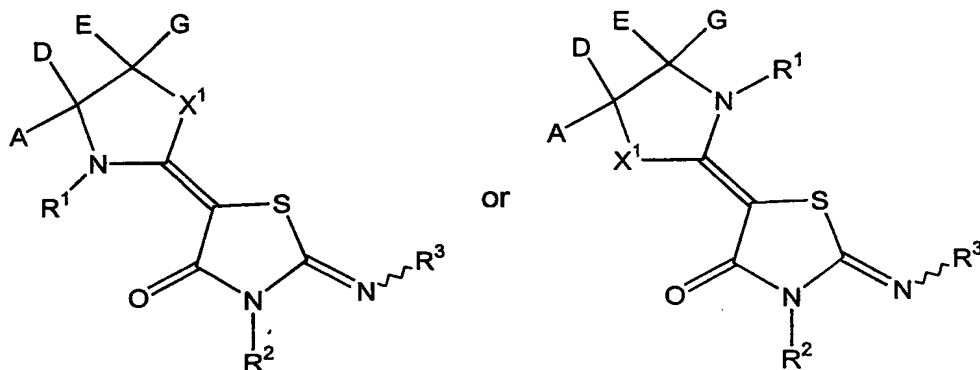
THF                      tetrahydrofuran  
 TFA                      trifluoroacetic acid

As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with  
 5 their common usage, recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature (see, (1972) *Biochem.* 11:942-944).

#### B. Heterocyclic Modulators of Nuclear Receptors

Compounds for use in compositions and methods for modulating the  
 10 activity of nuclear receptors are provided. In particular, compounds for use in compositions and methods for modulating farnesoid X receptor (FXR), liver X receptors (LXR $\alpha$  and LXR $\beta$ ) and/or orphan nuclear receptors, are provided.

In certain embodiments, the compounds are thiazolidinones, *i.e.*, compounds of formulae I where X<sup>2</sup> is S and X<sup>3</sup> is O, that are substituted with a  
 15 heterocyclylene group and an imine moiety. Thus, in these embodiments, the compounds have formulae II:



or a pharmaceutically acceptable derivative thereof, where A, D, E and G are selected from (i) or (ii) as follows:

- 20 (i) A and G are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted

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heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroarylium, substituted or unsubstituted heteroaryliumalkyl, halo, pseudohalo, OR<sup>10</sup>, SR<sup>10</sup>, S(=O)R<sup>13</sup>, S(=O)<sub>2</sub>R<sup>13</sup>, NR<sup>11</sup>R<sup>12</sup> and C(=J)R<sup>13</sup>, or A and G together form substituted or unsubstituted alkylene, substituted or unsubstituted azaalkylene, substituted or unsubstituted oxaalkylene, substituted or unsubstituted thiaalkylene, substituted or unsubstituted alkenylene, substituted or unsubstituted alkynylene, substituted or unsubstituted 1,3-butadienylene, substituted or unsubstituted 1-aza-1,3-butadienylene, or substituted or unsubstituted 2-aza-1,3-butadienylene;

D and E are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo and pseudohalo or D and E together form a bond; or

(ii) A and D; or E and G; together form substituted or unsubstituted alkylene, substituted or unsubstituted azaalkylene, substituted or unsubstituted oxaalkylene, or substituted or unsubstituted thiaalkylene;

and the others of A, D, E and G are selected as in (i);

X<sup>1</sup> is selected from O, S, S(=O), S(=O)<sub>2</sub>, Se, NR<sup>5</sup>, CR<sup>6</sup>R<sup>7</sup> and CR<sup>8</sup>=CR<sup>9</sup>; R<sup>1</sup> and R<sup>2</sup> are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or

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- unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroarylum, substituted or unsubstituted heteroarylumalkyl, OR<sup>10</sup>, SR<sup>10</sup>, S(=O)R<sup>13</sup>, S(=O)<sub>2</sub>R<sup>13</sup>, NR<sup>11</sup>R<sup>12</sup> and C(=J)R<sup>13</sup>; R<sup>3</sup> is hydrogen,
- 5 substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or
- 10 unsubstituted heteroarylum, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroarylumalkyl, OR<sup>10</sup>, SR<sup>10</sup>, S(=O)R<sup>13</sup>, S(=O)<sub>2</sub>R<sup>13</sup>, NR<sup>11</sup>R<sup>12</sup> and C(=J)R<sup>13</sup>; where:
- R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl,
- 15 substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo,
- 20 pseudohalo, OR<sup>10</sup>, NR<sup>14</sup>R<sup>15</sup> and C(=J)R<sup>13</sup>;
- R<sup>10</sup>, R<sup>11</sup> and R<sup>12</sup> are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl,
- 25 substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl or C(=J)R<sup>13</sup>;
- J is O, S or NR<sup>14</sup>;
- R<sup>13</sup> is selected from hydrogen, substituted or unsubstituted alkyl,
- 30 substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted

heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, pseudohalo, OR<sup>16</sup> and NR<sup>14</sup>R<sup>15</sup>;

- 5 R<sup>14</sup>, R<sup>15</sup> and R<sup>16</sup> are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl;

where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclalkyl, aryl, heteroaryl, heteroarylium, aralkyl,

- 10 heteroaralkyl and heteroaryliumalkyl moieties of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup> and R<sup>13</sup> are unsubstituted or substituted with one or more substituents each independently selected from Q<sup>1</sup>, where Q<sup>1</sup> is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, 20 alkoxycarbonylalkyl, aryloxy carbonyl, aryloxy carbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclioxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, 25 aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylamino carbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl- 30 N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-

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- dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, imino, hydroxyimino, alkoxyimino, aryloxyimino, aralkoxyimino, alkylazo, arylazo, aralkylazo, aminothiocarbonyl, alkylaminothiocarbonyl,
- 5 arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminomalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino,
- 10 aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclisulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio,
- 15 hydroxycarbonylalkylthio, thiocyno, isothiocyno, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylamino sulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl,
- 20 hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylamino sulfonyl or alkylarylaminosulfonyl; or two  $Q^1$  groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*,  $-O-(CH_2)_y-O-$ ), thioalkylenoxy (*i.e.*,  $-S-(CH_2)_y-O-$ ) or alkylenedithioxy (*i.e.*,  $-S-(CH_2)_y-S-$ ) where
- 25 y is 1 or 2; or two  $Q^1$  groups, which substitute the same atom, together form alkylene;
- each  $Q^1$  is independently unsubstituted or substituted with one or more substituents each independently selected from  $Q^2$ ;
- each  $Q^2$  is independently halo, pseudohalo, hydroxy, oxo, thia, nitrile,
- 30 nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2

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- doubl bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl,
- 5 heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxy carbonyl, aryloxy carbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy,
- 10 perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido,
- 15 N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-trialkylureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl,
- 20 alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylaminalkyl, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl,
- 25 aryloxy carbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxy carbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio,
- 30 perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy,

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hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl,

- 5 alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two Q<sup>2</sup> groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*, -O-(CH<sub>2</sub>)<sub>y</sub>-O-), thioalkylenoxy (*i.e.*, -S-(CH<sub>2</sub>)<sub>y</sub>-O-) or alkylenedithioxy (*i.e.*, -S-(CH<sub>2</sub>)<sub>y</sub>-S-) where y is 1 or 2; or two Q<sup>2</sup> groups, which substitute the same
- 10 atom, together form alkylene;

each Q<sup>2</sup> group is independently unsubstituted or substituted with one or more, in one embodiment one, two or three, substituents each independently selected from alkyl, halo and pseudohalo;

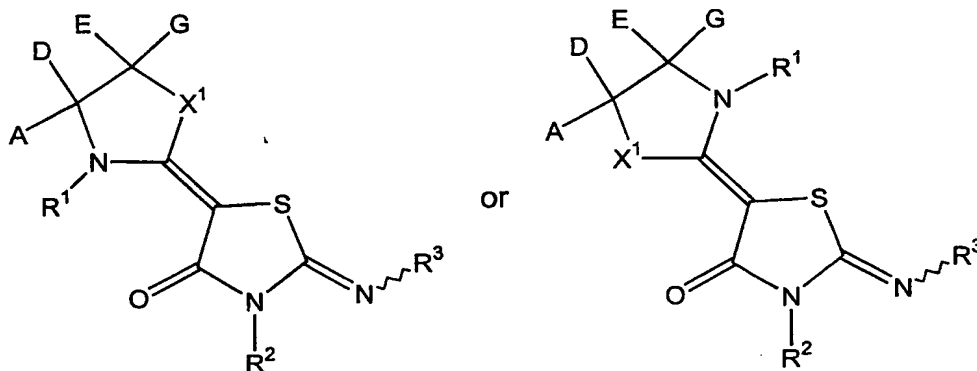
- R<sup>50</sup> is hydroxy, alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or
- 15 -NR<sup>70</sup>R<sup>71</sup>, where R<sup>70</sup> and R<sup>71</sup> are each independently hydrogen, alkyl, aralkyl, aryl, heteroaryl, heteroaralkyl or heterocyclyl, or R<sup>70</sup> and R<sup>71</sup> together form alkylene, azaalkylene, oxaalkylene or thiaalkylene;

R<sup>51</sup>, R<sup>52</sup> and R<sup>53</sup> are each independently hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl;

- 20 R<sup>60</sup> is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl;

R<sup>63</sup> is alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or -NR<sup>70</sup>R<sup>71</sup>.

In another embodiment, the compounds have formulae II:



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or a pharmaceutically acceptable derivative thereof, where A, D, E and G are selected from (i) or (ii) as follows:

- (i) A and G are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroarylum, substituted or unsubstituted heteroarylumalkyl, halo, pseudohalo,  $\text{OR}^{10}$ ,  $\text{SR}^{10}$ ,  $\text{S(=O)R}^{13}$ ,  $\text{S(=O)}_2\text{R}^{13}$ ,  $\text{NR}^{11}\text{R}^{12}$  and  $\text{C(=J)R}^{13}$ , or A and G together form substituted or unsubstituted alkylene, substituted or unsubstituted azaalkylene, substituted or unsubstituted oxalkylene, substituted or unsubstituted thiaalkylene, substituted or unsubstituted alkenylene, substituted or unsubstituted alkynylene, substituted or unsubstituted 1,3-butadienylene, substituted or unsubstituted 1-aza-1,3-butadienylene, or substituted or unsubstituted 2-aza-1,3-butadienylene;
- (ii) D and E are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo and pseudohalo or D and E together form a bond; or
- (ii) A and D; or E and G; together form substituted or unsubstituted alkylene, substituted or unsubstituted azaalkylene, substituted or



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unsubstituted oxaalkylene, or substituted or unsubstituted thiaalkylene;  
and the others of A, D, E and G are selected as in (i);

$X^1$  is selected from O, S,  $S(=O)$ ,  $S(=O)_2$ , Se,  $NR^5$ ,  $CR^6R^7$  and

$CR^8=CR^9$ ;  $R^1$  and  $R^2$  are each independently selected from hydrogen,

- 5 substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl,  
substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl,  
substituted or unsubstituted heterocyclyl, substituted or unsubstituted  
cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or  
unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or
- 10 unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or  
unsubstituted heteroarylium, substituted or unsubstituted heteroaryliumalkyl,  
 $OR^{10}$ ,  $SR^{10}$ ,  $S(=O)R^{13}$ ,  $S(=O)_2R^{13}$ ,  $NR^{11}R^{12}$  and  $C(=J)R^{13}$ ;  $R^3$  is hydrogen,  
substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl,  
substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl,
- 15 substituted or unsubstituted heterocyclyl, substituted or unsubstituted  
cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or  
unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or  
unsubstituted heteroarylium, substituted or unsubstituted aralkyl, substituted  
or unsubstituted heteroaralkyl, substituted or unsubstituted heteroaryliumalkyl,
- 20  $OR^{10}$ ,  $SR^{10}$ ,  $S(=O)R^{13}$ ,  $S(=O)_2R^{13}$ ,  $NR^{11}R^{12}$  and  $C(=J)R^{13}$ ; where:  
 $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$  and  $R^9$  are each independently selected from hydrogen,  
substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl,  
substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl,  
substituted or unsubstituted heterocyclyl, substituted or unsubstituted
- 25 cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or  
unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or  
unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo,  
pseudohalo,  $OR^{10}$ ,  $NR^{14}R^{15}$  and  $C(=J)R^{13}$ ;
- $R^{10}$ ,  $R^{11}$  and  $R^{12}$  are each independently hydrogen, substituted or
- 30 unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or  
unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or

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- unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl or  $C(=J)R^{13}$ ;
- 5 J is O, S or  $NR^{14}$ ;
- $R^{13}$  is selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or
- 10 unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, pseudohalo,  $OR^{16}$  and  $NR^{14}R^{15}$ ;
- $R^{14}$ ,  $R^{15}$  and  $R^{16}$  are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl,
- 15 heteroaryl, aralkyl and heteroaralkyl;
- where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, heteroarylium, aralkyl, heteroaralkyl and heteroaryliumalkyl moieties of  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$ ,  $R^9$ ,  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$  and  $R^{13}$  are unsubstituted or substituted with one or more
- 20 substituents each independently selected from  $Q^1$ , where  $Q^1$  is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl,
- 25 heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl,
- 30 dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy,

- heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, 5 alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, 10 N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, 15 alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxy carbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxy carbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroaryl sulfonylamino, heterocyclisulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , 20 dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, 25 dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two  $Q^1$  groups, which substitute atoms in a 1,2 or 30 1,3 arrangement, together form alkylenedioxy (*i.e.*,  $-O-(CH_2)_Y-O-$ ), thioalkylenoxy (*i.e.*,  $-S-(CH_2)_Y-O-$ ) or alkylenedithioxy (*i.e.*,  $-S-(CH_2)_Y-S-$ ) where



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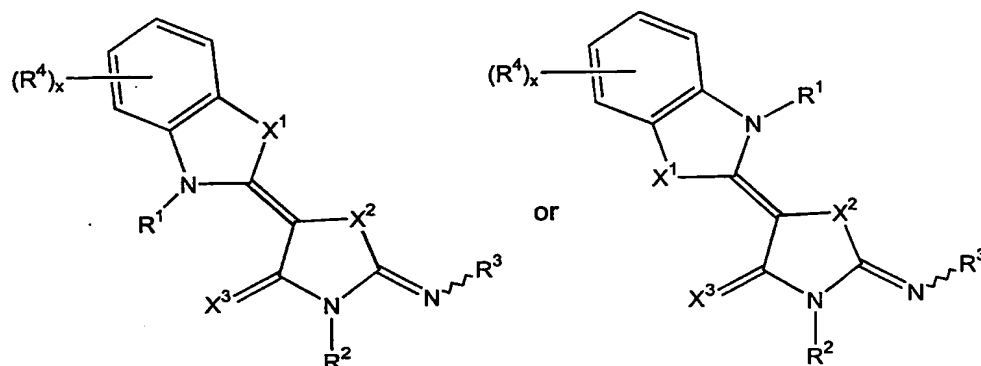
- aryloxycarbonylaminoalkyl, aryloxyarylcabonylamino, aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclisulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl,
- 5 alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy,
- 10 diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two  $Q^2$  groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy
- 15 (*i.e.*,  $-O-(CH_2)_y-O-$ ), thioalkylenoxy (*i.e.*,  $-S-(CH_2)_y-O-$ ) or alkylenedithioxy (*i.e.*,  $-S-(CH_2)_y-S-$ ) where  $y$  is 1 or 2; or two  $Q^2$  groups, which substitute the same atom, together form alkylene;
- $R^{50}$  is hydroxy, alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or  $-NR^{70}R^{71}$ , where  $R^{70}$  and  $R^{71}$  are each independently hydrogen, alkyl, aralkyl,
- 20 aryl, heteroaryl, heteroaralkyl or heterocyclyl, or  $R^{70}$  and  $R^{71}$  together form alkylene, azaalkylene, oxaalkylene or thiaalkylene;
- $R^{51}$ ,  $R^{52}$  and  $R^{53}$  are each independently hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl;
- $R^{60}$  is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl,
- 25 heterocyclyl or heterocyclylalkyl;
- $R^{63}$  is alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or  $-NR^{70}R^{71}$ .
- In another embodiment, A and G are each independently selected from hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted aryl, or together form substituted or unsubstituted 1,3-butadienyl. In a further
- 30 embodiment, A and G are each independently hydrogen, substituted or unsubstituted methyl, substituted or unsubstituted naphthyl, or substituted or

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unsubstituted phenyl, or together form 1,3-butadienyl. In another embodiment, A and G are both hydrogen.

In another embodiment, D and E are each hydrogen, or together form a bond.

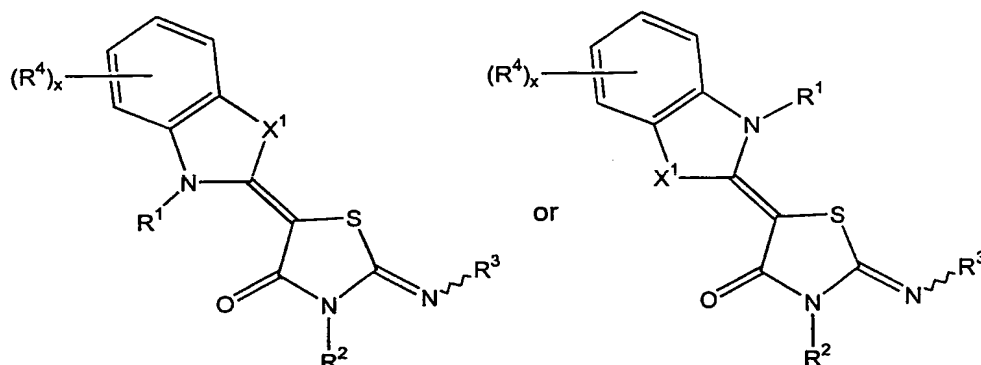
- 5 In another embodiment, the compounds for use in the compositions and methods provided herein have formulae I where D and E together form a bond, and A and G together form 1,3-butadienyl. Thus, in this embodiment, the compounds have formulae III:



- 10 or a pharmaceutically acceptable derivative thereof, where  $R^1$ ,  $R^2$ ,  $R^3$ ,  $X^1$ ,  $X^2$  and  $X^3$  are selected as above; each  $R^4$  is independently substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl,
- 15 substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted guanidino, substituted or unsubstituted isothioureido, halo, pseudohalo,  $OR^{10}$ ,  $SR^{10}$ ,  $S(=O)R^{13}$ ,  $S(=O)_2R^{13}$ ,  $NR^{11}R^{12}$  or  $C(=J)R^{13}$ ; x is an integer from 0 to 4;
- 20 and the amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, heteroarylium, aralkyl, heteroaralkyl and heteroaryliumalkyl moieties of  $R^4$  are unsubstituted or substituted with one or more substituents each independently selected from  $Q^2$ , as defined above.

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In another embodiment, the compounds for use in the compositions and methods provided herein have formulae IV:



- or a pharmaceutically acceptable derivative thereof, where  $R^1$ ,  $R^2$ ,  $R^3$ ,  $X^1$ ,  $X^2$  and  $X^3$  are selected as above; each  $R^4$  is independently substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted guanidino, substituted or unsubstituted isothioureido, halo, pseudohalo,  $OR^{10}$ ,  $SR^{10}$ ,  $S(=O)R^{13}$ ,  $S(=O)_2R^{13}$ ,  $NR^{11}R^{12}$  or  $C(=J)R^{13}$ ;  $x$  is an integer from 0 to 4; and the amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclalkyl, aryl, heteroaryl, heteroarylium, aralkyl, heteroaralkyl and heteroaryliumalkyl moieties of  $R^4$  are unsubstituted or substituted with one or more, in certain embodiments one to three or four, substituents each independently selected from  $Q^2$ , as defined above.

- In certain embodiments herein, the compounds are of formulae III or IV, and are selected with the proviso that when  $R^3$  is substituted or unsubstituted heteroarylium then the heteroatom substituent is not alkyl or aryl. In another embodiment, the compounds are of formulae III or IV, and are selected with the proviso that  $R^3$  is not substituted or unsubstituted heteroarylium or substituted or unsubstituted heteroaryliumalkyl. In other

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embodiments, the compounds are of formula III or IV and are selected with the proviso that  $R^3$  is not heteroaryl. In further embodiments, the compounds are of formula III or IV and are selected with the proviso that  $R^3$  is not alkyl. In another embodiment, the compounds are of formula III or IV and are selected  
5 with the proviso that  $R^3$  is not heterocycloaryl (*i.e.*, an aryl groups possessing a fused heterocyclic moiety).

In certain embodiments herein,  $X^1$  is O, S or  $NR^5$ . In other embodiments,  $X^1$  is O or S. In another embodiment,  $X^1$  is S.

In other embodiments,  $R^1$  is substituted or unsubstituted alkyl. In  
10 further embodiments,  $R^1$  is methyl.

In another embodiment,  $R^2$  is substituted or unsubstituted alkyl or substituted or unsubstituted aralkyl. In further embodiments,  $R^2$  is ethyl, n-butyl or benzyl. In another embodiment,  $R^2$  is benzyl. In another embodiment,  $R^2$  is substituted or unsubstituted heteroaralkyl. In another  
15 embodiment,  $R^2$  is pyridylmethyl. In another embodiment,  $R^2$  is picolyl (*i.e.*, 2-, 3-, or 4-pyridylmethyl). In another embodiment,  $R^2$  is 2-furylmethyl. In another embodiment,  $R^2$  is 3-pyridylmethyl.

In another embodiment,  $R^3$  is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. In further embodiments,  $R^3$  is  
20 substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted pyridyl, substituted or unsubstituted indazolyl, or substituted or unsubstituted quinolinyl. In another embodiment,  $R^3$  is substituted or unsubstituted quinolyl, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted isoquinolyl,  
25 substituted or unsubstituted pyridyl, or substituted or unsubstituted indazolyl. In certain embodiments,  $R^3$  is substituted or unsubstituted phenyl or substituted or unsubstituted naphthyl. In another embodiment,  $R^3$  is substituted or unsubstituted phenyl.

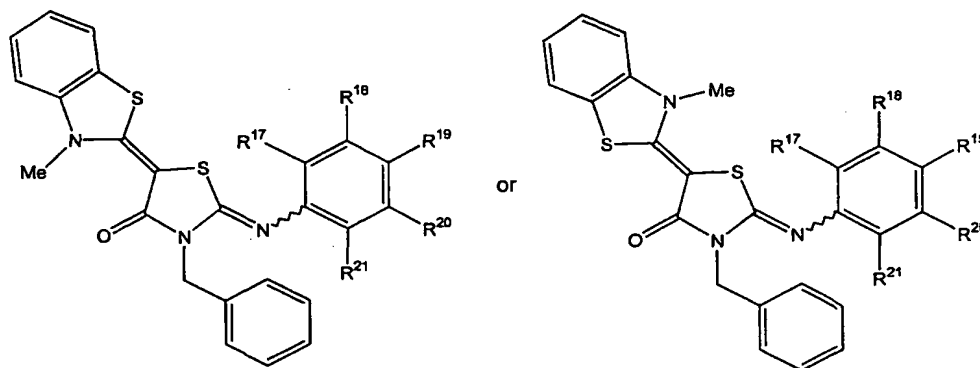
In another embodiment,  $Q^1$  is selected from halo, hydroxy, nitrile, nitro,  
30 hydroxycarbonyl, alkyl, haloalkyl, polyhaloalkyl, heteroaryl, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkoxy, perfluoroalkoxy, aralkoxy,



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- hydroxyimino, alkoxyimino, aralkoxyimino, arylazo, haloalkylcarbonylamino, amino, alkylamino, dialkylamino, haloalkylamino, alkylcarbonylamino, dialkylcarbonyloxy or heterocyclyl; or two Q<sup>1</sup> groups, which substitute atoms in a 1,2 arrangement, form alkylenedioxy. In another embodiment, Q<sup>1</sup> is
- 5 selected from halo, hydroxy, nitrile, nitro, hydroxycarbonyl, alkyl, haloalkyl, polyhaloalkyl, heteroaryl, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkoxy, perfluoroalkoxy, aralkoxy, amino, alkylamino, dialkylamino, haloalkylamino, alkylcarbonylamino, dialkylcarbonyloxy or heterocyclyl; or two Q<sup>1</sup> groups, which substitute atoms in a 1,2 arrangement, form alkylenedioxy.
- 10 In further embodiments, Q<sup>1</sup> is methoxy, dimethylamino, NH<sub>2</sub>, benzyloxy, hydroxy, CN, isopropyl, methyl, nitro, ethylamino, trifluoromethyl, acetyl, chloro, n-propyl, ethoxy, methylcarbonylamino, CONH<sub>2</sub>, methoxycarbonyl, methylamino, trifluoromethoxy, imidazolyl, hydroxycarbonyl, isopropylamino, tert-butylamino, 2,2,2-trifluoroethylamino, piperidiny, dimethylaminocarbonyloxy, 2-hydroxyethoxy, 2-(N-morpholinyl)ethoxy or morpholinyl, or two Q<sup>1</sup> groups, which substitute atoms in a 1,2 arrangement, form methylenedioxy. In another embodiment, Q<sup>1</sup> is hydroxycarbonyl or ethylamino.

- In further embodiments, the compounds for use in the compositions
- 20 and methods provided herein are of formulae IV where x is 0, R<sup>1</sup> is methyl, R<sup>2</sup> is benzyl, X<sup>1</sup> is S and R<sup>3</sup> is a substituted or unsubstituted phenyl group. Thus, in these embodiments, the compounds have formulae V:



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- or a pharmaceutically acceptable derivative thereof, where  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  are each independently selected from hydrogen, halo, pseudohalo, hydroxyl, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl,
- 5 alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkylidiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl,
- 10 aryloxy carbonyl, aryloxy carbonylalkyl, aralkoxy carbonyl, aralkoxy carbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy,
- 15 alkoxycarbonyloxy, aryloxy carbonyloxy, aralkoxy carbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-
- 20 aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, aminothiocabonyl, alkylaminothiocabonyl, arylaminothiocabonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino,
- 25 diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxy carbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxy carbonylaminoalkyl, aryloxy arylcarbonylamino, aryloxy carbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,
- 30  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio,

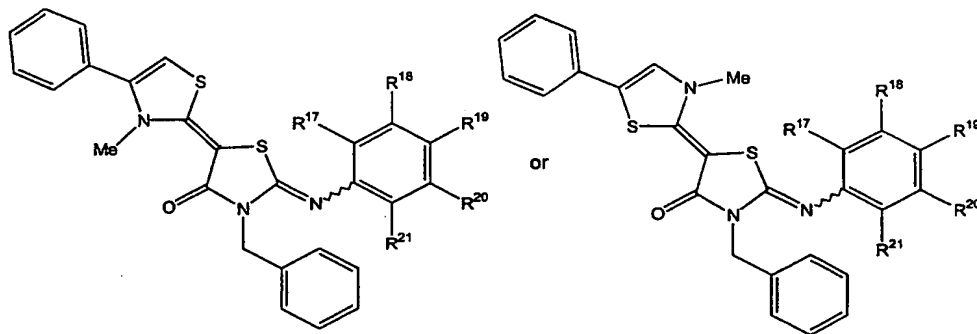
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- perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy,
- 5 diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl, or any two of  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$ , which substitute adjacent carbons on the ring, together form
- 10 alkylenedioxy; and
- the aryl and heteroaryl groups of  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  are unsubstituted or substituted with one or more substituents, in one embodiment one to three or four substituents, each independently selected from  $R^{30}$ , where  $R^{30}$  is alkyl, halo, pseudohalo, alkoxy, aryloxy or
- 15 alkylenedioxy.
- In another embodiment,  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  are each independently selected from hydrogen, halo, hydroxy, nitrile, nitro, hydroxycarbonyl, alkyl, haloalkyl, polyhaloalkyl, heteroaryl, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkoxy, perfluoroalkoxy, aralkoxy, amino,
- 20 alkylamino, dialkylamino, haloalkylamino, alkylcarbonylamino or heterocyclyl; or any two of  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$ , which substitute adjacent carbons on the ring, form alkylenedioxy. In further embodiments,  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  are each independently hydrogen, methoxy, dimethylamino,  $NH_2$ , benzyloxy, hydroxy, CN, isopropyl, methyl, nitro, ethylamino, trifluoromethyl,
- 25 acetyl, chloro, n-propyl, ethoxy, methylcarbonylamino,  $CONH_2$ , methoxycarbonyl, methylamino, trifluoromethoxy, imidazolyl, hydroxycarbonyl, isopropylamino, tert-butylamino, 2,2,2-trifluoroethylamino, piperidinyl or morpholinyl, or any two of  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$ , which substitute adjacent carbons on the ring, form methylenedioxy.

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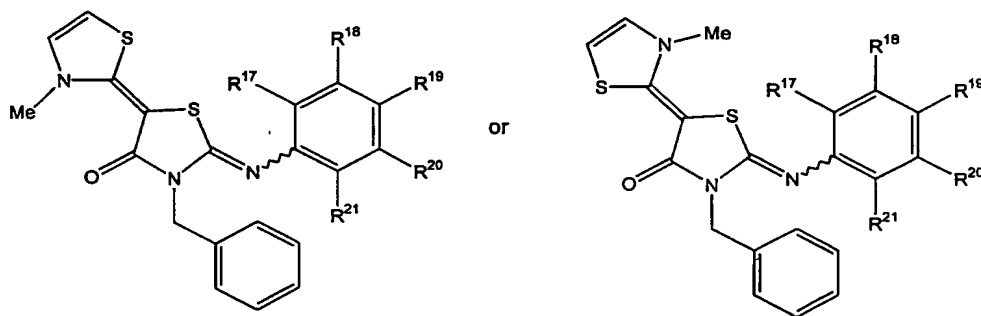
In another embodiment, A is phenyl which is unsubstituted or is substituted with one or more, in one embodiment, one, two or three, groups each independently selected from Q<sup>1</sup>.

- 5 In another embodiment, the compounds for use in the compositions and methods provided herein have formulae II where X<sup>1</sup> is S; R<sup>1</sup> is methyl; R<sup>2</sup> is benzyl; A is phenyl; G is hydrogen; and D and E together form a bond. Thus, in this embodiment, the compounds have formulae VI:



- 10 or a pharmaceutically acceptable derivative thereof, where R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup> and R<sup>21</sup> are selected as above.

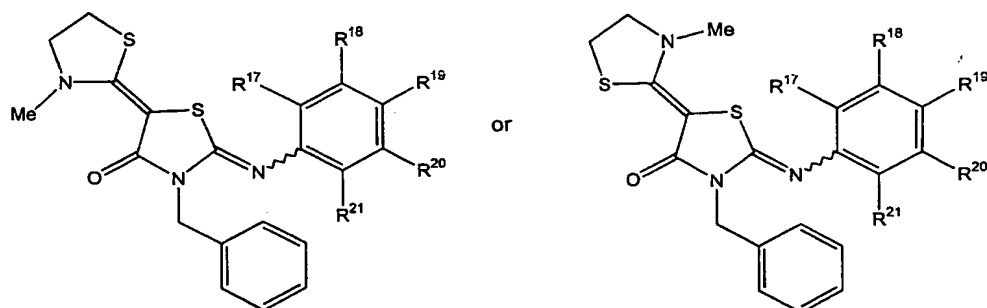
In another embodiment, the compounds for use in the compositions and methods provided herein have formulae II where X<sup>1</sup> is S; R<sup>1</sup> is methyl; R<sup>2</sup> is benzyl; A and G are hydrogen; and D and E together form a bond. Thus, in this embodiment, the compounds have formulae VII:



- 15 or a pharmaceutically acceptable derivative thereof, where R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup> and R<sup>21</sup> are selected as above.

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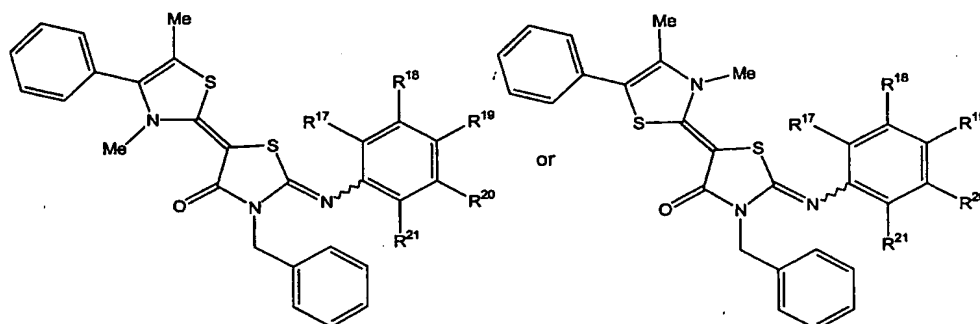
In another embodiment, the compounds for use in the compositions and methods provided herein have formulae II where  $X^1$  is S;  $R^1$  is methyl;  $R^2$  is benzyl; and A, G, D and E are hydrogen. Thus, in this embodiment, the compounds have formulae VIII:



5

or a pharmaceutically acceptable derivative thereof, where  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  are selected as above.

In another embodiment, the compounds for use in the compositions and methods provided herein have formulae II where  $X^1$  is S;  $R^1$  is methyl;  $R^2$  is benzyl; A is phenyl; G is methyl; and D and E together form a bond. Thus, in this embodiment, the compounds have formulae IX:



or a pharmaceutically acceptable derivative thereof, where  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  are selected as above.

15

In another embodiment, the compounds provided herein have formulae V-XI, where  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  are each independently selected from (i) or (ii) as follows:

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(i)  $R^{21}$  is ethylamino;  $R^{18}$  is cyano; and  $R^{17}$ ,  $R^{19}$  and  $R^{20}$  are each hydrogen; or

(ii)  $R^{17}$  is ethylamino;  $R^{20}$  is cyano; and  $R^{18}$ ,  $R^{19}$  and  $R^{21}$  are each hydrogen.

- 5 In certain embodiments, the compounds have formulae I, where  $X^1$ ,  $X^2$  and  $X^3$  are selected from (i) or (ii) as follows: (i)  $X^1$ ,  $X^2$  and  $X^3$  are each independently S, O or  $NR^5$ ; or (ii)  $X^1$  is  $-CR^8=CR^9-$ , where  $R^8$  and  $R^9$  are as defined herein, and  $X^2$  and  $X^3$  are each independently S, O or  $NR^5$ ;  $R^1$  is substituted or unsubstituted alkyl, where there are 0 to 6 substituents selected
- 10 from alkoxy, alkoxyalkyl, hydroxycarbonyl, alkylcarbonyloxy, hydroxy, halo, pseudohalo, aryl and heteroaryl;  $R^2$  is substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaralkyl, or substituted or unsubstituted
- 15 heterocyclalkyl; where there are 0 or 1 substituents selected from alkoxy and hydroxycarbonyl;  $R^3$  is substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl, or substituted or unsubstituted aralkyl; where there are 0 to 5 substituents selected from alkylamino, cyano, cycloalkyl, hydroxy, alkoxy, dialkylamino, amino, heterocycl, aralkoxy, alkyl,
- 20 nitro, haloalkyl, alkylcarbonyl, halo, alkylcarbonylamino, alkoxyalkylcarbonylamino, dialkylaminoalkylcarbonylamino, aminocarbonyl, alkoxyalkylcarbonyl, aralkylamino, cycloalkylamino, heterocyclamino, haloalkylamino, haloalkoxy, hydroxycarbonyl, aminosulfonyl, alkylcarbonylaminosulfonyl, or haloalkylcarbonylamino, or any two substituents, which substitute atoms in a
- 25 1,2 or 1,3 arrangement, together form alkylenedioxy; A and G are each independently selected from hydrogen, substituted or unsubstituted aryl, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxyalkyl, hydroxycarbonyl, and substituted or unsubstituted alkylcarbonyl, where there are 0 to 5 substituents selected from aryl, haloalkyl, haloalkoxy, nitro, halo,
- 30 pseudohalo, hydroxy, alkyl and alkoxy, or A and G together form substituted or unsubstituted alkylene, substituted or unsubstituted azaalkylene or

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- substituted or unsubstituted 1,3-butadienylene, in one embodiment substituted or unsubstituted alkylene, where there are 0 to 4 substituents selected from halo, pseudohalo, alkoxy, nitro, haloalkyl, alkylcarbonylamino, hydroxy, alkylaminocarbonyloxy, alkoxy carbonylalkoxy, aminocarbonylalkoxy, hydroxyalkoxy, alkyl, haloalkylaminocarbonyloxy and alkylaminoalkoxy; D and E are each hydrogen, or together form a bond; and R<sup>5</sup> is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo, pseudohalo, OR<sup>10</sup>, SR<sup>10</sup>, S(=O)R<sup>13</sup>, S(=O)<sub>2</sub>R<sup>13</sup>, NR<sup>14</sup>R<sup>15</sup> or C(=J)R<sup>13</sup>; R<sup>10</sup> is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl or C(=J)R<sup>13</sup>; J is O, S or NR<sup>14</sup>; R<sup>13</sup> is selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, pseudohalo, OR<sup>16</sup> and NR<sup>14</sup>R<sup>15</sup>; R<sup>14</sup>, R<sup>15</sup> and R<sup>16</sup> are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl; where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl moieties of R<sup>5</sup>, R<sup>10</sup> and R<sup>13</sup> are

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- unsubstituted or substituted with one or more substituents each independently selected from Q<sup>1</sup>, where Q<sup>1</sup> is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2
- 5 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl,
- 10 aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy,
- 15 arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido,
- 20 N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, imino, hydroxyimino, alkoxyimino, aralkoxyimino, arylazo, haloalkylcarbonylamino,
- 25 aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylaminalkyl, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino,
- 30 arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino,



heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio,

- 5 hydroxycarbonylalkylthio, thiocyno, isothiocyno, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylamino sulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl
- 10 hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylamino sulfonyl or alkylarylaminosulfonyl; or two Q<sup>1</sup> groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy, thioalkylenoxy or alkylenedithioxy; or two Q<sup>1</sup> groups, which substitute the same atom, together
- 15 form alkylene; each Q<sup>1</sup> is independently unsubstituted or substituted with one or more substituents each independently selected from Q<sup>2</sup>; each Q<sup>2</sup> is independently halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double
- 20 bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxy carbonyl, aryloxy carbonylalkyl,
- 25 aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylamino carbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy,
- 30 alkoxycarbonyloxy, aryloxy carbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy,

- alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, aminothiocabonyl, alkylaminothiocabonyl, arylaminothiocabonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminominoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido,
- 15  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy,
- 20 alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylamino sulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylamino sulfonyl or
- 25 alkylarylaminosulfonyl; or two  $Q^2$  groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*,  $-O-(CH_2)_y-O-$ ), thioalkylenoxy (*i.e.*,  $-S-(CH_2)_y-O-$ ) or alkylenedithioxy (*i.e.*,  $-S-(CH_2)_y-S-$ ) where  $y$  is 1 or 2; or two  $Q^2$  groups, which substitute the same atom, together form alkylene;
- 30  $R^{50}$  is hydroxy, alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or  $-NR^{70}R^{71}$ , where  $R^{70}$  and  $R^{71}$  are each independently hydrogen, alkyl, aralkyl,

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aryl, heteroaryl, heteroaralkyl or heterocyclyl, or  $R^{70}$  and  $R^{71}$  together form alkylene, azaalkylene, oxaalkylene or thiaalkylene;

$R^{51}$ ,  $R^{52}$  and  $R^{53}$  are each independently hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclalkyl;

- 5  $R^{60}$  is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclalkyl;

$R^{63}$  is alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or  $-NR^{70}R^{71}$ .

- In certain embodiments, the compounds have formulae I, where  $X^1$ ,  $X^2$  and  $X^3$  are each independently S, O or  $NR^5$ ;  $R^1$  is substituted or unsubstituted
- 10 alkyl, where there are 0 to 6 substituents selected from halo, pseudohalo, aryl and heteroaryl;  $R^2$  is substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaralkyl, or substituted or unsubstituted heterocyclalkyl;
- 15 where there are 0 or 1 substituents selected from alkoxycarbonyl and hydroxycarbonyl;  $R^3$  is substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl, or substituted or unsubstituted aralkyl; where there are 0 to 5 substituents selected from alkylamino, cyano, cycloalkyl, hydroxy, alkoxy, dialkylamino, amino, heterocyclyl, aralkoxy, alkyl, nitro, haloalkyl,
- 20 alkylcarbonyl, halo, alkylcarbonylamino, aminocarbonyl, alkoxycarbonyl, aralkylamino, cycloalkylamino, heterocyclylamino, haloalkylamino, haloalkoxy, hydroxycarbonyl, aminosulfonyl, alkylcarbonylaminosulfonyl, or haloalkylcarbonylamino, or any two substituents, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylendioxy; A and G are each
- 25 independently selected from hydrogen, substituted or unsubstituted aryl, substituted or unsubstituted alkyl and substituted or unsubstituted alkylcarbonyl, where there are 0 to 5 substituents selected from nitro, halo, pseudohalo, alkyl and alkoxy, or A and G together form substituted or unsubstituted alkylene or substituted or unsubstituted 1,3-butadienylene, in
- 30 one embodiment substituted or unsubstituted alkylene, where there are 0 to 4 substituents selected from halo, pseudohalo, alkoxy, nitro, haloalkyl,

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- alkylcarbonylamino, hydroxy, alkylaminocarbonyloxy, alkoxycarbonylalkoxy, aminocarbonylalkoxy, hydroxyalkoxy, alkyl, haloalkylaminocarbonyloxy and alkylaminoalkoxy; D and E are each hydrogen, or together form a bond; and  $R^5$  is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted
- 5** alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl,
- 10** halo, pseudohalo,  $OR^{10}$ ,  $SR^{10}$ ,  $S(=O)R^{13}$ ,  $S(=O)_2R^{13}$ ,  $NR^{14}R^{15}$  or  $C(=J)R^{13}$ ;  $R^{10}$  is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl,
- 15** substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl or  $C(=J)R^{13}$ ; J is O, S or  $NR^{14}$ ;  $R^{13}$  is selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl,
- 20** substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, pseudohalo,  $OR^{16}$  and  $NR^{14}R^{15}$ ;  $R^{14}$ ,  $R^{15}$  and  $R^{16}$  are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl,
- 25** heterocyclalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl; where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl moieties of  $R^5$ ,  $R^{10}$  and  $R^{13}$  are unsubstituted or substituted with one or more substituents each independently
- 30** selected from  $Q^1$ , where  $Q^1$  is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl,

- haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyl diarylsilyl,
- 5 triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy,
- 10 aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy,
- 15 guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-
- 20 triarylureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino,
- 25 aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroaryl sulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl,
- 30 alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano,

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- alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylamino sulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, 5 arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylamino sulfonyl or alkylarylaminosulfonyl; or two Q<sup>1</sup> groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy, thioalkylenoxy or alkylenedithioxy; or two Q<sup>1</sup> groups, which substitute the 10 same atom, together form alkylene; each Q<sup>1</sup> is independently unsubstituted or substituted with one or more substituents each independently selected from Q<sup>2</sup>; each Q<sup>2</sup> is independently halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 15 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, 20 aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylamino carbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, 25 arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylamino carbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, 30 N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-

- diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl,
- 5 alkylarylaminominoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxy carbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxy carbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroaryl sulfonylamino,
- 10 heterocyclisulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy,
- 15 hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylamino sulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl,
- 20 diarylamino sulfonyl or alkylarylaminosulfonyl; or two  $Q^2$  groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*,  $-O-(CH_2)_y-O-$ ), thioalkylenoxy (*i.e.*,  $-S-(CH_2)_y-O-$ ) or alkylenedithioxy (*i.e.*,  $-S-(CH_2)_y-S-$ ) where  $y$  is 1 or 2; or two  $Q^2$  groups, which substitute the same atom, together form alkylene;
- 25  $R^{50}$  is hydroxy, alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or  $-NR^{70}R^{71}$ , where  $R^{70}$  and  $R^{71}$  are each independently hydrogen, alkyl, aralkyl, aryl, heteroaryl, heteroaralkyl or heterocyclyl, or  $R^{70}$  and  $R^{71}$  together form alkylene, azaalkylene, oxaalkylene or thiaalkylene;
- $R^{51}$ ,  $R^{52}$  and  $R^{53}$  are each independently hydrogen, alkyl, aryl, aralkyl,
- 30 heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl;

R<sup>60</sup> is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl;

R<sup>63</sup> is alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or -NR<sup>70</sup>R<sup>71</sup>.

In certain embodiments, the compounds claimed herein exhibit

- 5 improved *in vitro* activity, efficacy, potency and/or pharmacokinetic properties, such as solubility, oral half-life, bioavailability, oral absorption, and/or *in vivo* activity, over related commercially available compounds or related compounds disclosed previously.

- In certain embodiments, A and G are selected with the proviso that A  
10 and G are not both methyl. In another embodiment, A and G together form butadienyl with the proviso that the resulting benzo-fused group is not substituted at the 5-position with methoxy or chloro and is not substituted at the 6-position with methoxy or methyl. In another embodiment, A and G together form butadienyl with the proviso that the resulting benzo-fused group  
15 is not substituted at the 5-position with alkoxy or halo and is not substituted at the 6-position with alkoxy or alkyl. In another embodiment, A and G together form butadienyl with the proviso that the resulting benzo-fused group is not substituted with methoxy, methyl or chloro. In another embodiment, A and G together form butadienyl with the proviso that the resulting benzo-fused group  
20 is not substituted with alkoxy, alkyl or halo.

In another embodiment, X<sup>1</sup> is S. In another embodiment, X<sup>1</sup> is -CR<sup>8</sup>=CR<sup>9</sup>-. In another embodiment, X<sup>2</sup> is S. In another embodiment, X<sup>3</sup> is O.

- In another embodiment, R<sup>1</sup> is substituted alkyl. In another embodiment, R<sup>1</sup> is 2-methoxy-1-ethyl, 3-methoxy-1-propyl,  
25 methoxycarbonylmethyl, hydroxycarbonylmethyl, 2-acetoxy-1-ethyl or 2-hydroxy-1-ethyl. In another embodiment, R<sup>1</sup> is unsubstituted alkyl. In other embodiments, R<sup>1</sup> is methyl.

- In another embodiment, R<sup>2</sup> is benzyl, phenyl, allyl, ethyl, butyl, cyclohexyl, propyl, 3-pyridylmethyl, 2-furylmethyl, 4-methoxycarbonylbenzyl,  
30 4-hydroxycarbonylbenzyl, 2-phenethyl or 2-(4-morpholinyl)ethyl. In another embodiment, R<sup>2</sup> is benzyl. In another embodiment, R<sup>2</sup> is pyridylmethyl. In



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another embodiment, R<sup>2</sup> is picolyl (*i.e.*, 2-, 3-, or 4-pyridylmethyl). In another embodiment, R<sup>2</sup> is 2-furylmethyl. In another embodiment, R<sup>2</sup> is 3-pyridylmethyl.

- In another embodiment, R<sup>3</sup> is substituted or unsubstituted quinolyl,
- 5 substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted isoquinolyl, substituted or unsubstituted pyridyl, or substituted or unsubstituted indazolyl. In another embodiment, R<sup>3</sup> is substituted or unsubstituted phenyl. In other embodiments, R<sup>3</sup> is substituted with 0 to 5 substituents selected from ethylamino, cyano, cyclohexyl, hydroxy,
- 10 methoxy, dimethylamino, amino, 4-morpholinyl, methylamino, isopropylamino, benzyloxy, methyl, isopropyl, nitro, trifluoromethyl, methylcarbonyl, chloro, propyl, ethoxy, methylcarbonylamino, aminocarbonyl, methoxycarbonyl, methoxymethylcarbonylamino, dimethylaminomethylcarbonylamino, butylamino, benzylamino, cyclopentylamino, 1-pyrrolidinylamino, pyrrolidinyl,
- 15 t-butylamino, 2,2,2-trifluoroethylamino, piperidinyl, trifluoromethoxy, hydroxycarbonyl, aminosulfonyl, methylcarbonylaminosulfonyl, trifluoromethylcarbonylamino and t-butoxycarbonyl, or any two substituents, which substitute atoms in a 1,2 arrangement, together form methylenedioxy. In further embodiments, R<sup>3</sup> is 5-quinolyl, 2-ethylamino-5-cyanophenyl, 4-
- 20 cyclohexylphenyl, 2-hydroxy-1-naphthyl, 6-quinolyl, 3-methoxyphenyl, 4-dimethylaminophenyl, 4-aminophenyl, 4-(4-morpholinyl)phenyl, 2-methylamino-5-cyanophenyl, 2-dimethylamino-5-cyanophenyl, 2-ethylaminophenyl, 3-cyanophenyl, 2-aminophenyl, 2-isopropylamino-5-cyanophenyl, 4-benzyloxyphenyl, 2-methyl-4-hydroxy-5-isopropylphenyl, 2-
- 25 ethylamino-5-nitrophenyl, 3-trifluoromethylphenyl, 3-methylcarbonylphenyl, 3-chlorophenyl, 2-propylphenyl, 2-ethoxyphenyl, 3-methylcarbonylamino-phenyl, 3-aminocarbonylphenyl, 3-methoxycarbonylphenyl, 8-quinolyl, 8-hydroxy-5-quinolyl, 2-butylamino-5-cyanophenyl, 2-benzylamino-5-cyanophenyl, 2-cyclopentylamino-5-cyanophenyl, 2-(1-pyrrolidinyl)amino-5-cyanophenyl, 5-
- 30 isoquinolyl, 1-isoquinolyl, 4-methylcarbonylamino-phenyl, 2-t-butylamino-5-cyanophenyl, 2-(2,2,2-trifluoroethyl)amino-5-cyanophenyl, 2-piperidinyl-5-

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- cyanophenyl, 4-methylcarbonylphenyl, 4-aminocarbonylphenyl, 2-ethylamino-5-methoxymethylcarbonylaminophenyl, 2-ethylamino-5-dimethylaminomethylcarbonylaminophenyl, 1-naphthyl, 2-naphthyl, 2-pyridyl, 3-pyridyl, 2-ethoxy-5-methylcarbonylaminophenyl, 4-pyridyl, 4-methoxycarbonylphenyl, 4-
- 5 trifluoromethoxyphenyl, 5-indazolyl, 4-(imidazol-1-yl)phenyl, 3,4-methylenedioxyphenyl, 3-hydroxycarbonylphenyl, 2-ethylamino-5-methylcarbonylphenyl, 4-aminosulfonylphenyl, 4-methylcarbonylaminosulfonylphenyl, 3-methylcarbonylphenyl, 2-methylcarbonylamino-5-pyridyl, 4-cyano-3-methylcarbonylaminophenyl, 2-
- 10 methylamino-5-methylcarbonylphenyl, 4-trifluoromethylcarbonylaminophenyl, 2-ethylamino-5-methoxycarbonylphenyl, 2-hydroxycarbonylphenyl or 2-ethylamino-5-t-butoxycarbonylphenyl.

- In another embodiment, A and G are each independently selected from hydrogen, substituted or unsubstituted phenyl, substituted or unsubstituted
- 15 methyl, substituted or unsubstituted naphthyl, hydroxycarbonyl, substituted and unsubstituted ethoxycarbonyl, and substituted or unsubstituted methylcarbonyl, or A and G together from substituted or unsubstituted butylene, substituted or unsubstituted propylene, substituted or unsubstituted methyleneazaethylene, or substituted or unsubstituted 1,3-butadienylene. In
- 20 other embodiments, A and G are each independently selected from hydrogen, substituted or unsubstituted phenyl, substituted or unsubstituted methyl, substituted or unsubstituted naphthyl, and substituted or unsubstituted methylcarbonyl, and are substituted with 0 to 4 substituents selected from chloro, bromo, methoxy, fluoro, ethoxy, nitro, trifluoromethylcarbonylamino,
- 25 dimethylaminocarbonyloxy, 2-(1-piperidinyl)ethoxy, 2-(1-methyl-4-piperazinyl)ethoxy, 2-(N-morpholinyl)ethoxy, 2-dimethylaminoethoxy, hydroxycarbonylmethoxy, methylcarbonylamino, phenyl, trifluoromethyl, trifluoromethoxy, hydroxy, ethylaminocarbonyloxy, methoxycarbonylmethoxy, aminocarbonylmethoxy, 2-hydroxyethoxy, 2-hydroxypropoxy, methyl, 2-
- 30 chloroethylaminocarbonyloxy and 2-methylaminoethoxy. In further embodiments, A and G together form substituted or unsubstituted 1,3-

- butadienylene and are substituted with 0 to 5 substituents selected from nitro, fluoro, chloro, methyl and methoxy. In another embodiment, A and G are each independently selected from hydrogen, 4-phenylphenyl, 4-trifluoromethylphenyl, 2-trifluoromethylphenyl, 4-trifluoromethoxyphenyl, 4-nitrophenyl, 4-fluorophenyl, 4-chlorophenyl, 4-methylphenyl, 4-methoxyphenyl, methyl, 2-naphthyl, 4-bromophenyl, 2-methoxyphenyl, 3-fluorophenyl, 2,4-dimethoxyphenyl, ethoxycarbonyl, benzyl, hydroxycarbonyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, phenyl and methylcarbonyl, or A and G together form 1,3-butadienylene, 2-chloro-1,3-butadienylene, 2-methoxy-1,3-butadienylene, 2-fluoro-1,3-butadienylene, 2-ethoxy-1,3-butadienylene, 2-nitro-1,3-butadienylene, 2-trifluoromethyl-1,3-butadienylene, 2-trifluoromethoxy-1,3-butadienylene, 2-methylcarbonylamino-1,3-butadienylene, 2-trifluoromethylcarbonylamino-1,3-butadienylene, 2-aminocarbonylmethoxy-1,3-butadienylene, 2-(2-hydroxyethoxy)-1,3-butadienylene, 2-(3-hydroxypropoxy)-1,3-butadienylene, 2-dimethylaminocarbonyloxy-1,3-butadienylene, 2-(1-piperidinyloxy)-1,3-butadienylene, 2-(4-(1-methylpiperazinyl)ethoxy)-1,3-butadienylene, 2-(4-morpholinyl)ethoxy-1,3-butadienylene, 2-dimethylaminoethoxy-1,3-butadienylene, 2-hydroxycarbonylmethoxy-1,3-butadienylene, 2-hydroxy-1,3-butadienylene, 2-ethylaminocarbonyloxy-1,3-butadienylene, 2-methoxycarbonylmethoxy-1,3-butadienylene, 2-aminocarbonylmethoxy-1,3-butadienylene, 2-(2-hydroxyethoxy)-1,3-butadienylene, 1-methoxy-1,3-butadienylene, 1-methyl-1,3-butadienylene, 1-chloro-1,3-butadienylene, 2-(2-chloroethylaminocarbonyloxy)-1,3-butadienylene or 2-(2-methylaminoethoxy)-1,3-butadienylene.

In another embodiment, D and E are each hydrogen or together form a bond.

- In certain embodiments herein, the compounds are selected from the following compounds. In other embodiments, the compounds are selected from those disclosed in the Examples. All isomers of these compounds are within the scope of the disclosure herein:

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- 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-phenylimino-thiazolidine-4-one;
- 3-benzyl-2-(4-methoxyphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;
- 5 3-benzyl-2-(4-dimethylaminophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;
- 2-(4-aminophenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;
- 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(quinolin-6-ylimino)-
- 10 thiazolidine-4-one;
- 2-(2-aminophenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;
- 3-benzyl-2-(4-benzyloxyphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;
- 15 3-benzyl-2-(2-hydroxy-1-naphthylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;
- 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile;
- 3-benzyl-2-(4-hydroxy-5-isopropyl-2-methylphenylimino)-5-(3-methyl-3*H*-
- 20 benzothiazol-2-ylidene)thiazolidine-4-one;
- 3-benzyl-2-(2-ethylamino-5-nitrophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;
- 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-[3-(trifluoromethyl)-phenylimino]thiazolidine-4-one;
- 25 2-(3-acetylphenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;
- 3-benzyl-2-(3-chlorophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;
- 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-propyl-
- 30 phenylimino)thiazolidine-4-one;

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- 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(quinolin-5-ylimino)-thiazolidine-4-one;
- 3-benzyl-2-(2-ethoxyphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;
- 5 *N*-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}acetamide;
- 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzamide;
- 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzoic acid, methyl ester;
- 10 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(pyridin-3-ylimino)-thiazolidine-4-one;
- N*-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethoxyphenyl}acetamide;
- 15 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(pyridin-4-ylimino)-thiazolidine-4-one;
- 4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzoic acid, methyl ester;
- 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-[4-(trifluoro-
- 20 methoxy)phenylimino]thiazolidine-4-one;
- 3-benzyl-2-(1*H*-indazol-5-ylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-thiazolidin-4-one;
- 3-benzyl-2-(4-imidazol-1-ylphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;
- 25 2-(benzo[1,3]dioxol-5-ylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;
- 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzoic acid;
- 3-benzyl-2-[2-(ethylamino)phenylimino]-5-(3-methyl-3*H*-benzothiazol-2-
- 30 ylidene)thiazolidine-4-one;

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- 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(methylamino)benzonitrile;  
3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(ethylamino)benzonitrile;
- 5 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(isopropylamino)benzonitrile;  
3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(dimethylamino)benzonitrile;  
3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(*tert*-butylamino)benzonitrile;
- 10 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(2,2,2-trifluoroethylamino)benzonitrile;  
3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-piperidin-1-ylbenzonitrile;
- 15 2-[5-acetyl-2-(ethylamino)phenylimino]-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;  
3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(quinolin-6-ylimino)-thiazolidin-4-one;  
3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-morpholin-4-yl-phenylimino)thiazolidin-4-one;
- 20 3-[3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(methylamino)benzonitrile;  
4-dimethylamino-3-[3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile;
- 25 4-ethylamino-3-[3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile;  
3-[3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(isopropylamino)benzonitrile;  
3-[3-butyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile;
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- 3-benzyl-5-(3-methyl-3*H*-benzoxazol-2-ylidene)-2-(quinolin-5-ylimino)-thiazolidin-4-one;  
*N*-[4-(3'-benzyl-3-methyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-[2,5']-bithiazolyliden-2'-ylideneamino)phenyl]acetamide;
- 5 2'-[5-acetyl-2-(ethylamino)phenylimino]-3'-benzyl-3-methyl-4-phenyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one;  
3-(3'-benzyl-3-methyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-[2,5']bithiazol-yliden-2'-ylideneamino)-4-(ethylamino)benzonitrile;  
*N*-[4-(3'-benzyl-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)phenyl]acetamide;
- 10 *N*-[4-(3'-benzyl-3-methyl-4'-oxo-[2,5']bithiazolidinyliden-2'-ylideneamino)phenyl]acetamide;  
3-(3'-benzyl-3,5-dimethyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-[2,5']-bithiazolyliden-2'-ylideneamino)-4-(ethylamino)benzonitrile;
- 15 4-ethylamino-3-[3-benzyl-5-(3-methyl-5-chloro-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
3-phenyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-cyclohexylphenyl)imino-thiazolidine-4-one;  
3-allyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-hydroxy-1-naphthyl)imino-
- 20 thiazolidine-4-one;  
4-ethylamino-3-[3-phenyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(3-methyl-5-methoxy-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 25 3-allyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(5-quinolyl)imino-thiazolidine-4-one;  
4-ethylamino-3-[3-allyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
3-phenyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-benzylimino-thiazolidine-4-
- 30 one;

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-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(8-quinolyl)imino-  
ine-4-one;

-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(8-hydroxy-5-  
imino-thiazolidine-4-one;

-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(5-isoquinolyl)imino-  
ne-4-one;

-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(1-isoquinolyl)imino-  
ne-4-one;

-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-  
rbonylamino)phenylimino-thiazolidine-4-one;

-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-  
rbonyl)phenylimino-thiazolidine-4-one;

-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-  
bonyl)phenylimino-thiazolidine-4-one;

-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(1-naphthyl)imino-  
re-4-one;

-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-naphthyl)imino-  
re-4-one;

-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-pyridyl)imino-  
re-4-one;

-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-  
onyl)phenylimino-thiazolidine-4-one;

-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-  
bonylaminosulfonyl)phenylimino-thiazolidine-4-one;

-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(3-  
bonyl)phenylimino-thiazolidine-4-one;

-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-methylcarbonylamino-5-  
no-thiazolidine-4-one;

-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-cyano-5-  
bonylamino)phenyl)imino-thiazolidine-4-one;



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- 4-ethylamino-3-[3-benzyl-5-(6-ethoxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 4-ethylamino-3-[3-benzyl-5-(6-nitro-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 5 4-ethylamino-3-[3-benzyl-5-(5-trifluoromethyl-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 4-ethylamino-3-[3-benzyl-5-(6-methylcarbonylamino-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 4-ethylamino-3-[3-benzyl-5-(5-hydroxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 10 4-ethylamino-3-[3-benzyl-5-(6-hydroxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 4-ethylamino-3-[3-benzyl-5-(5-ethylaminocarbonyloxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 15 4-ethylamino-3-[3-benzyl-5-(5-methoxycarbonylmethoxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 4-ethylamino-3-[3-benzyl-5-(5-aminocarbonylmethoxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 4-ethylamino-3-[3-benzyl-5-(5-(2-hydroxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 20 4-ethylamino-3-[3-benzyl-5-(4-methoxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 4-ethylamino-3-[3-benzyl-5-(4-methyl-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 25 4-ethylamino-3-[3-benzyl-5-(4-chloro-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 4-ethylamino-3-[3-benzyl-5-(5-(2-chloroethylaminocarbonyloxy)-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 4-ethylamino-3-[3-benzyl-5-(5-(2-methylaminoethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 30 4-ethylamino-3-[3-benzyl-5-(5-(2-methylaminoethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;

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- 4-ethylamino-3-[3-propyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
3-(3-pyridylmethyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(3-acetylphenyl)imino-thiazolidine-4-one;
- 5 3-(3-pyridylmethyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-ethylamino-5-acetylphenyl)imino-thiazolidine-4-one;  
4-ethylamino-3-[3-(3-pyridylmethyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-(2-furylmethyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 10 3-(4-methoxycarbonylbenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-ethylamino-5-acetylphenyl)imino-thiazolidine-4-one;  
3-(4-hydroxycarbonylbenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-ethylamino-5-acetylphenyl)imino-thiazolidine-4-one;
- 15 4-ethylamino-3-[3-(2-phenylethyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-(2-(4-morpholinyl)-1-ethyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
3-benzyl-5-(3-methylthiazolin-2-ylidene)-2-(4-methylcarbonylaminophenyl)imino-thiazolidine-4-one;
- 20 3-benzyl-5-(3-methyl-4-phenylthiazol-2-ylidene)-2-(4-methylcarbonylaminophenyl)imino-thiazolidine-4-one;  
3-benzyl-5-(3-methyl-4-phenylthiazol-2-ylidene)-2-(2-ethylamino-5-acetylphenyl)imino-thiazolidine-4-one;
- 25 3-benzyl-5-(3-methylthiazol-2-ylidene)-2-(4-methylcarbonylaminophenyl)imino-thiazolidine-4-one;  
4-ethylamino-3-[3-benzyl-5-(3-methyl-4-phenylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(3-methyl-4,5-dimethylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
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- 4-ethylamino-3-[3-benzyl-5-(3-methyl-4-phenyl-5-methylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 4-ethylamino-3-[3-benzyl-5-(3-methyl-4,5-butylenylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 5 4-ethylamino-3-[3-benzyl-5-(3-methyl-4-ethylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 4-ethylamino-3-[3-benzyl-5-(3-methyl-4-(4-nitrophenyl)thiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 4-ethylamino-3-[3-benzyl-5-(3-methyl-4-(4-fluorophenyl)thiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 10 4-ethylamino-3-[3-benzyl-5-(3-methyl-4-(4-chlorophenyl)thiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 4-ethylamino-3-[3-benzyl-5-(3-methyl-4-(4-methylphenyl)thiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 15 4-ethylamino-3-[3-benzyl-5-(3-methyl-4-(4-methoxyphenyl)thiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 4-ethylamino-3-[3-benzyl-5-(3-methyl-4-methyl-5-acetylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 4-ethylamino-3-[3-benzyl-5-(3-methyl-4,5-propylenylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 20 4-ethylamino-3-[3-benzyl-5-(3-methyl-4,5-diphenylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 4-ethylamino-3-[3-benzyl-5-(3-methyl-4-methylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 25 4-ethylamino-3-[3-(3-pyridylmethyl)-5-(3-methyl-4,5-butylenylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile; and
- 3-(4-methoxycarbonylbenzyl)-5-(3-methyl-4,5-butylenylthiazol-2-ylidene)-2-(2-ethylamino-5-acetylphenyl)imino-thiazolidine-4-one.

- In certain embodiments herein, the compounds provided herein are
- 30 FXR or LXR antagonists. In these embodiments, the compounds have formulae I, where A and G are each independently substituted or

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- unsubstituted phenyl, substituted or unsubstituted naphthyl, or substituted or unsubstituted methyl, substituted or unsubstituted ethyl or together form substituted or unsubstituted butadienylene where there are 0 to 4 substituents, in one embodiment 0 or 1 substituents, selected from
- 5 methylcarbonylamino, hydroxy, trifluoromethoxy, trifluorocarbonylamino, aminocarbonylmethoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, dimethylaminocarbonyloxy, 2-(1-piperidinyl)ethoxy, 2-(4-(1-methylpiperazin)yl)ethoxy, 2-(4-morpholinyl)ethoxy, 2-dimethylaminoethoxy and hydroxycarbonylmethoxy; D and E form a bond; X<sup>1</sup> and X<sup>2</sup> are both S; X<sup>3</sup>
- 10 is O; R<sup>1</sup> is methyl; R<sup>2</sup> is benzyl; and R<sup>3</sup> is 5-cyano-2-ethylaminophenyl.

In certain embodiments, FXR or LXR antagonists provided herein are selected from the following compounds. All isomer of these compounds are within the scope of the disclosure herein:

- 3-(3'-Benzyl-3,5-dimethyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-
- 15 [2,5']bithiazolyliden-2'-ylideneamino)-4-ethylamino-benzonitrile;
- 3-(3'-Benzyl-5-ethyl-3-methyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-
- [2,5']bithiazolyliden-2'-ylideneamino)-4-ethylamino-benzonitrile;
- 3-(3'-Benzyl-3-methyl-4-naphthalen-2-yl-4'-oxo-3',4'-dihydro-3*H*-
- [2,5']bithiazolyliden-2'-ylideneamino)-4-ethylamino-benzonitrile;
- 20 3-[3'-Benzyl-4-(4-bromophenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-
- [2,5']bithiazolyliden-2'-ylideneamino]-4-ethylamino-benzonitrile;
- 3-[3'-Benzyl-4-(2-methoxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-
- [2,5']bithiazolyliden-2'-ylideneamino]-4-ethylamino-benzonitrile;
- 3-[3'-Benzyl-4-(3-fluorophenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-
- 25 [2,5']bithiazolyliden-2'-ylideneamino]-4-ethylamino-benzonitrile;
- 3-[3'-Benzyl-4-(2,4-dimethoxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-
- [2,5']bithiazolyliden-2'-ylideneamino]-4-ethylamino-benzonitrile;
- N*-(2-[3-Benzyl-2-(5-cyano-2-ethylamino-phenylimino)-4-oxo-thiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl)-acetamide;
- 30 3-[3-Benzyl-5-(6-hydroxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]-4-ethylamino-benzonitrile;

- 3-[3-Benzyl-5-(3-methyl-6-trifluoromethoxy-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]-4-ethylamino-benzonitrile;  
*N*-(2-[3-Benzyl-2-(5-cyano-2-ethylamino-phenylimino)-4-oxo-thiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl)-2,2,2-trifluoroacetamide;  
 5 2-{2-[3-Benzyl-2-(5-cyano-2-ethylamino-phenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yloxy}-acetamide;  
 3-{3-Benzyl-5-[5-(2-hydroxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylamino-benzonitrile;  
 3-{3-Benzyl-5-[5-(3-hydroxypropoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylamino-benzonitrile;  
 10 Dimethylcarbamic acid 2-[3-benzyl-2-(5-cyano-2-ethylamino-phenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yl ester;  
 3-{3-Benzyl-5-[3-methyl-5-(2-piperidin-1-ylethoxy)-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylamino-benzonitrile;  
 15 3-(3-Benzyl-5-[3-methyl-5-[2-(4-methylpiperazin-1-yl)-ethoxy]-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino)-4-ethylamino-benzonitrile;  
 3-{3-Benzyl-5-[3-methyl-5-(2-morpholin-4-ylethoxy)-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylamino-benzonitrile;  
 20 3-{3-Benzyl-5-[5-(2-dimethylaminoethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylamino-benzonitrile; and  
 {2-[3-Benzyl-2-(5-cyano-2-ethylamino-phenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yloxy}-acetic acid.

- In another embodiment, the compounds for use in the compositions  
 25 and methods provided herein are shown in the Examples. All isomers of these compounds are within the scope of this disclosure.

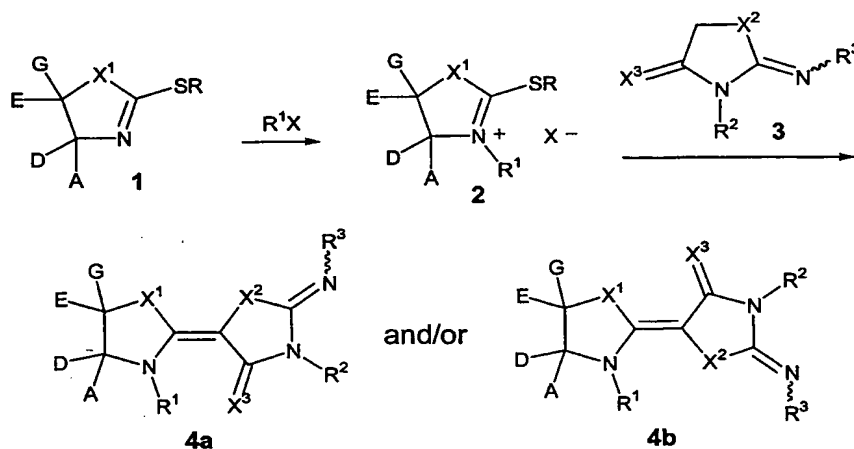
### C. Preparation of the compounds

- Starting materials in the synthesis examples provided herein are either available from commercial sources or via literature procedures. All  
 30 commercially available compounds were used without further purification unless otherwise indicated. CDCl<sub>3</sub> (99.8% D, Cambridge Isotope

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Laboratories) was used in all experiments as indicated. Proton ( $^1\text{H}$ ) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. Significant peaks are tabulated and typically include: number of protons, and multiplicity (s, singlet; d, double; t, triplet; q, quartet; m, multiplet; br s, broad singlet). Chemical shifts are reported as parts per million ( $\delta$ ) relative to tetramethylsilane. Low-resolution mass spectra (MS) were obtained as electrospray ionization (ESI) mass spectra, which were recorded on a Perkin-Elmer SCIEX HPLC/MS instrument using reverse-phase conditions (acetonitrile/water, 0.05% trifluoroacetic acid). Flash chromatography was performed using Merck Silica Gel 60 (230-400 mesh) following standard protocol (Still *et al.* (1978) *J. Org. Chem.* 43, 2923).

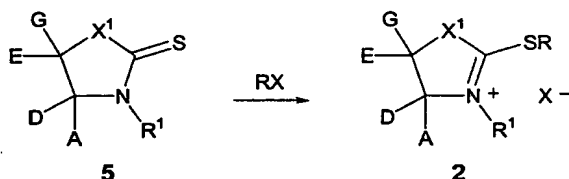
The following illustrations depict general preparations of compounds claimed herein and consist of reactions typically known to one skilled in the art of chemical synthesis. The substituents A, D, E, G,  $\text{R}^1$ - $\text{R}^3$  and  $\text{X}^1$ - $\text{X}^3$  have been previously described. Also it will be apparent to one skilled in the art that many of the products could exist as one or more isomers, that is E/Z isomers, enantiomers and/or diastereomers.



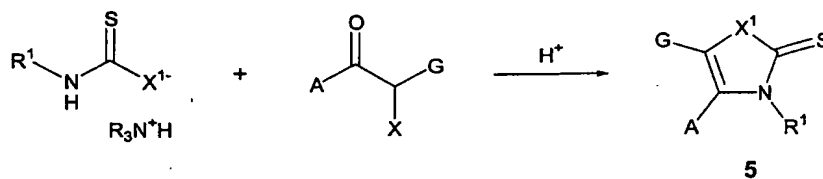
As shown above, treatment of 2-(alkylthio)azole (1) with an alkylating agent ( $\text{R}^1\text{X}$ ) affords the corresponding 2-(alkylthio)azolium complex (2), which then is condensed with 2-iminoazolidine (3) in the presence of a base to yield heterocycle (4). Thus, for example, when 1 is a 1,3-heterocycle such as

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- thiazole ( $X^1 = S$ ; E and D form a bond) that is alkylated with methyl *p*-toluenesulfonate, an intermediate *N*-methyl thiazolium complex **2** is prepared (see, e.g., U.S. Patent Nos. 5,707,794 and 2,388,963). Subsequently, for example, when **3** is an 2-iminothiazolidinone ( $X^2 = S$  and  $X^3 = O$ ), an 2-imino-
- 5** 5-(thiazol-2-ylidene)thiazolidin-4-one **4** is generated. Likewise, other heterocycles **1**, such as but not limited to thiazoles, thiazolines, benzimidazoles, benzoxazoles, quinolines, pyridines and indoles, should undergo this transformation when bearing a 2-alkylthio or 2-mercapto substituent.
- 10** The synthesis of intermediate **2** is alternatively prepared from the corresponding thione precursor (**5**) upon alkylation with RX. For example, when **5** is thiazolin-2-thione ( $X^1 = S$ ) that is alkylated with methyl *p*-toluenesulfonate (RX), an intermediate *N*-alkyl 2-(thiomethyl)thiazolinium complex **2** is generated.

**15**

- Furthermore, for example, when the thione precursor **5** is thiazole-2-thione ( $X^1 = S$ ; E and D form a bond), it can be prepared by the condensation of a dithiocarbamate salt ( $X^1 = S$ ) with a  $\alpha$ -haloketone, as depicted below (see, e.g., Bellec *et al.* (1999) *Chem. Mater.* 11:3147; Humphlett *et al.* (1964) *J. Org. Chem.* 29:2146). Various dithiocarbamate salts are synthesized, for example, by reacting a primary amine, e.g., methylamine, with carbon disulfide in the presence of a base such as  $\text{Et}_3\text{N}$  (see, e.g., Humphlett *et al.* (1964) *J. Org. Chem.* 29:2146). The thiazole-2-thione **5** can then be transformed into the corresponding thiazolium complex **2**.

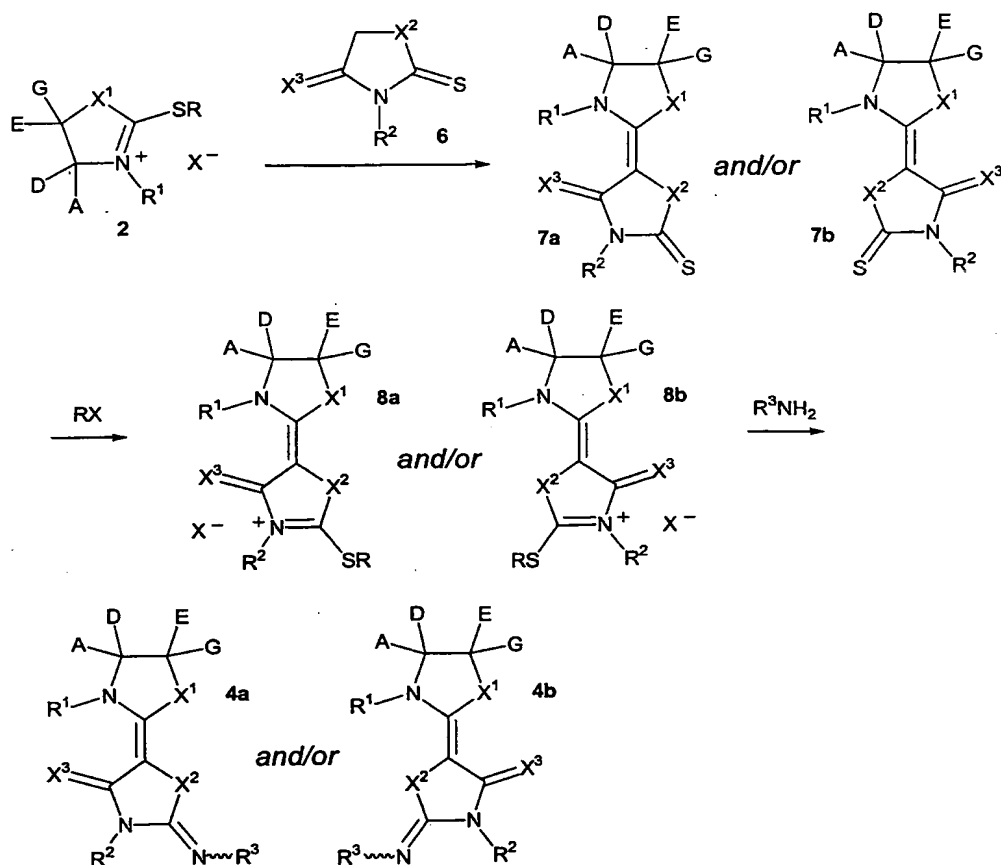
**25**

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- Alternatively, as depicted below, reaction of intermediate **2** with azolidin-2-thione (**6**) in the presence of base gives another azolidin-2-thione (**7**). Treatment of intermediate **7** with an alkylating agent (RX) affords the 2-(alkylthio)azolium complex (**8**), which reacts with an amine in the presence of
- 5 base to yield heterocycle **4**. Thus, for example, when **6** is a 1,3-heterocycle such as rhodanine ( $X^2 = S$  and  $X^3 = O$ ) that is condensed with an intermediate *N*-methyl benzothiazolium complex **2** ( $X^1 = S$ ; E and D form a bond; A and G form a fused benzene), a 5-(benzothiazol-2-ylidene)thiazolidin-4-one-2-thione **7** is generated (see, e.g., U.S. Patent Nos. 5,618,831 and 2,454,629).
- 10 Subsequently intermediate **7** is alkylated with, for example, methyl *p*-toluenesulfonate to give a 5-(benzothiazol-2-ylidene)-2-methylthio-4-oxothiazolidinium complex **8**, which can react with, for example, an aniline to yield an 2-imino-5-(benzothiazol-2-ylidene)thiazolidin-4-one **4** (see, e.g., U.S. Patent No. 5,618,831).

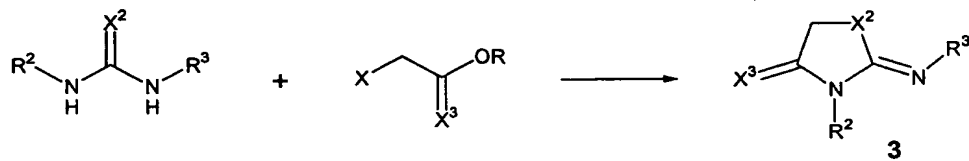


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In general, 2-iminoazolidines **3** may be prepared as depicted below.

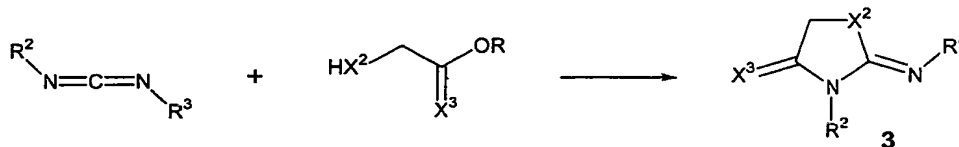
- Thus, for example, when **3** is an 2-imino-4-thiazolidinone (X<sup>2</sup> = S and X<sup>3</sup> = O),  
**5** it can be prepared by condensing a thiourea (X<sup>2</sup> = S) with a 2-haloester (X<sup>3</sup> = O) in the presence of base, in which R<sup>3</sup> is typically aryl or heteroaryl (see, e.g., Seada *et al.* (1993) *Indian J. Heterocycl. Chem.* 3:81; and International Patent Application Publication No. WO 00/42031).



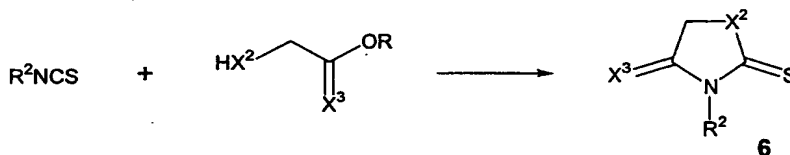
- 10** Likewise 2-iminoazolidines **3** may be prepared from a carbodiimide as depicted below. For example, when **3** is an 2-imino-4-imidazolidinone (X<sup>2</sup> =

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NR and  $X^3 = O$ ), it can be prepared by reacting a carbodiimide with a 2-aminoester ( $X^2 = NR$  and  $X^3 = O$ ). Also an 2-imino-4-oxazolidinones ( $X^2$  and  $X^3 = O$ ) can be prepared from a carbodiimide and a 2-hydroxyester.



- 5 Similarly azolidine-2-thiones **6** may be prepared as depicted below. Thus, for example, when **6** is a rhodanine ( $X^2 = S$  and  $X^3 = O$ ), it can be prepared by condensing an isothiocyanate with a 2-mercaptoester (see, *e.g.*, Dogan *et al.* (1992) *Tetrahedron* 48:7157; and Drobnica *et al.* (1972) *Chem. Zvesti* 26:538). Also imidazolidin-4-one-2-thiones ( $X^2 = NR$  and  $X^3 = O$ ) or
- 10 oxazolidin-4-one-2-thiones ( $X^2$  and  $X^3 = O$ ) can be prepared by reacting an isothiocyanate with 2-aminoester or 2-hydroxyester, respectively.



- Alkyl and aryl isothiocyanates, aryl amines, rhodanines, unsymmetrical carbodiimides and thioureas may be synthesized utilizing known methodology
- 15 (see, *e.g.*, Katritzky *et al.* (1984) *Comprehensive Heterocyclic Chemistry*; Pergamon Press: Oxford, UK; Katritzky *et al.* (2000) *Handbook of Heterocyclic Chemistry*, 2<sup>nd</sup> Ed.; Pergamon Press: Oxford, UK; March *Advanced Organic Chemistry*, 4<sup>th</sup> Ed.; John Wiley: New York (1992); and International Patent Application Publication No. WO 00/42031). For example,
- 20 alkyl and aryl isothiocyanates are readily prepared from reaction of an amine with thiophosgene or a thiophosgene equivalent, *e.g.* thiocarbonyl diimidazole. Many isothiocyanates also are commercially available. Unsymmetrical thioureas are prepared from reaction of an isothiocyanate with an amine.

**D. Formulation of pharmaceutical compositions**

The pharmaceutical compositions provided herein contain therapeutically effective amounts of one or more of the nuclear receptor activity modulators provided herein that are useful in the prevention,

- 5 treatment, or amelioration of one or more of the symptoms of diseases or disorders associated with nuclear receptor activity, including FXR, LXR and/or orphan nuclear receptor activity. Such diseases or disorders include, but are not limited to, hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin
- 10 conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, hyperlipidemia, cholestasis, peripheral occlusive disease, ischemic stroke, conditions of
- 15 disturbed differentiation or excess proliferation of the epidermis or mucous membrane, and cardiovascular disorders.

The compositions contain one or more compounds provided herein.

The compounds are preferably formulated into suitable pharmaceutical preparations such as solutions, suspensions, tablets, dispersible tablets, pills,

- 20 capsules, powders, sustained release formulations or elixirs, for oral administration or in sterile solutions or suspensions for parenteral administration, as well as transdermal patch preparation and dry powder inhalers. Typically the compounds described above are formulated into pharmaceutical compositions using techniques and procedures well known in
- 25 the art (see, e.g., Ansel *Introduction to Pharmaceutical Dosage Forms, Fourth Edition* 1985, 126).

In the compositions, effective concentrations of one or more compounds or pharmaceutically acceptable derivatives is (are) mixed with a suitable pharmaceutical carrier or vehicle. The compounds may be

- 30 derivatized as the corresponding salts, esters, enol ethers or esters, acids, bases, solvates, hydrates or prodrugs prior to formulation, as described

- above. The concentrations of the compounds in the compositions are effective for delivery of an amount, upon administration, that treats, prevents, or ameliorates one or more of the symptoms of diseases or disorders associated with nuclear receptor activity or in which nuclear receptor activity is
- 5 implicated. Such diseases or disorders include, but are not limited to, hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation,
- 10 immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, hyperlipidemia, cholestasis, peripheral occlusive disease, ischemic stroke, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, and cardiovascular disorders.
- 15 Typically, the compositions are formulated for single dosage administration. To formulate a composition, the weight fraction of compound is dissolved, suspended, dispersed or otherwise mixed in a selected vehicle at an effective concentration such that the treated condition is relieved or ameliorated. Pharmaceutical carriers or vehicles suitable for administration of
- 20 the compounds provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration.
- In addition, the compounds may be formulated as the sole pharmaceutically active ingredient in the composition or may be combined with other active ingredients. Liposomal suspensions, including tissue-
- 25 targeted liposomes, such as tumor-targeted liposomes, may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art. For example, liposome formulations may be prepared as described in U.S. Patent No. 4,522,811. Briefly, liposomes such as multilamellar vesicles (MLV's) may be formed by
- 30 drying down egg phosphatidyl choline and brain phosphatidyl serine (7:3 molar ratio) on the inside of a flask. A solution of a compound provided herein

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in phosphate buffered saline lacking divalent cations (PBS) is added and the flask shaken until the lipid film is dispersed. The resulting vesicles are washed to remove unencapsulated compound, pelleted by centrifugation, and then resuspended in PBS.

- 5           The active compound is included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the patient treated. The therapeutically effective concentration may be determined empirically by testing the compounds in *in vitro* and *in vivo* systems described herein and in
- 10 International Patent Application Publication Nos. 99/27365 and 00/25134 (see, e.g., EXAMPLES 53 and 54) and then extrapolated therefrom for dosages for humans.

- The concentration of active compound in the pharmaceutical composition will depend on absorption, inactivation and excretion rates of the
- 15 active compound, the physicochemical characteristics of the compound, the dosage schedule, and amount administered as well as other factors known to those of skill in the art. For example, the amount that is delivered is sufficient to ameliorate one or more of the symptoms of diseases or disorders associated with nuclear receptor activity or in which nuclear receptor activity is
- 20 implicated, as described herein.

- Typically a therapeutically effective dosage should produce a serum concentration of active ingredient of from about 0.1 ng/ml to about 50-100 µg/ml. The pharmaceutical compositions typically should provide a dosage of from about 0.001 mg to about 2000 mg of compound per kilogram of body
- 25 weight per day. Pharmaceutical dosage unit forms are prepared to provide from about 1 mg to about 1000 mg and preferably from about 10 to about 500 mg of the essential active ingredient or a combination of essential ingredients per dosage unit form.

- The active ingredient may be administered at once, or may be divided
- 30 into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of

the disease being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any

5 particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

10 Pharmaceutically acceptable derivatives include acids, bases, enol ethers and esters, salts, esters, hydrates, solvates and prodrug forms. The derivative is selected such that its pharmacokinetic properties are superior to the corresponding neutral compound.

Thus, effective concentrations or amounts of one or more of the  
15 compounds described herein or pharmaceutically acceptable derivatives thereof are mixed with a suitable pharmaceutical carrier or vehicle for systemic, topical or local administration to form pharmaceutical compositions. Compounds are included in an amount effective for ameliorating one or more symptoms of, or for treating or preventing diseases or disorders associated  
20 with nuclear receptor activity or in which nuclear receptor activity is implicated, as described herein. The concentration of active compound in the composition will depend on absorption, inactivation, excretion rates of the active compound, the dosage schedule, amount administered, particular formulation as well as other factors known to those of skill in the art.

25 The compositions are intended to be administered by a suitable route, including orally, parenterally, rectally, topically and locally. For oral administration, capsules and tablets are presently preferred. The compositions are in liquid, semi-liquid or solid form and are formulated in a manner suitable for each route of administration. Preferred modes of  
30 administration include parenteral and oral modes of administration. Oral administration is presently most preferred.

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- Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include any of the following components: a sterile diluent, such as water for injection, saline solution, fixed oil, polyethylene glycol, glycerine, propylene glycol or other synthetic solvent;
- 5 antimicrobial agents, such as benzyl alcohol and methyl parabens; antioxidants, such as ascorbic acid and sodium bisulfite; chelating agents, such as ethylenediaminetetraacetic acid (EDTA); buffers, such as acetates, citrates and phosphates; and agents for the adjustment of tonicity such as sodium chloride or dextrose. Parenteral preparations can be enclosed in
- 10 ampules, disposable syringes or single or multiple dose vials made of glass, plastic or other suitable material.

- In instances in which the compounds exhibit insufficient solubility, methods for solubilizing compounds may be used. Such methods are known to those of skill in this art, and include, but are not limited to, using cosolvents,
- 15 such as dimethylsulfoxide (DMSO), using surfactants, such as TWEEN®, or dissolution in aqueous sodium bicarbonate. Derivatives of the compounds, such as prodrugs of the compounds may also be used in formulating effective pharmaceutical compositions.

- Upon mixing or addition of the compound(s), the resulting mixture may
- 20 be a solution, suspension, emulsion or the like. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the disease, disorder or condition treated and may be empirically
- 25 determined.

- The pharmaceutical compositions are provided for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, and oral
- 30 solutions or suspensions, and oil-water emulsions containing suitable quantities of the compounds or pharmaceutically acceptable derivatives thereof. The pharmaceutically therapeutically active compounds and

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- derivatives thereof are typically formulated and administered in unit-dosage forms or multiple-dosage forms. Unit-dose forms as used herein refers to physically discrete units suitable for human and animal subjects and packaged individually as is known in the art. Each unit-dose contains a
- 5 predetermined quantity of the therapeutically active compound sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carrier, vehicle or diluent. Examples of unit-dose forms include ampoules and syringes and individually packaged tablets or capsules. Unit-dose forms may be administered in fractions or multiples thereof. A
- 10 multiple-dose form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dose form. Examples of multiple-dose forms include vials, bottles of tablets or capsules or bottles of pints or gallons. Hence, multiple dose form is a multiple of unit-doses which are not segregated in packaging.
- 15 The composition can contain along with the active ingredient: a diluent such as lactose, sucrose, dicalcium phosphate, or carboxymethylcellulose; a lubricant, such as magnesium stearate, calcium stearate and talc; and a binder such as starch, natural gums, such as gum acaciagelatin, glucose, molasses, polyvinylpyrrolidone, celluloses and derivatives thereof, povidone,
- 20 crospovidones and other such binders known to those of skill in the art. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, or otherwise mixing an active compound as defined above and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, glycols, ethanol, and
- 25 the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting agents, emulsifying agents, or solubilizing agents, pH buffering agents and the like, for example, acetate, sodium citrate, cyclodextrine derivatives, sorbitan monolaurate,
- 30 triethanolamine sodium acetate, triethanolamine oleate, and other such agents. Actual methods of preparing such dosage forms are known, or will be



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apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 15th Edition, 1975. The composition or formulation to be administered will, in any event, contain a quantity of the active compound in an amount sufficient to

5 alleviate the symptoms of the treated subject.

Dosage forms or compositions containing active ingredient in the range of 0.005% to 100% with the balance made up from non-toxic carrier may be prepared. For oral administration, a pharmaceutically acceptable non-toxic composition is formed by the incorporation of any of the normally employed

10 excipients, such as, for example pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, talcum, cellulose derivatives, sodium crosscarmellose, glucose, sucrose, magnesium carbonate or sodium saccharin. Such compositions include solutions, suspensions, tablets, capsules, powders and sustained release formulations, such as, but not

15 limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers, such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid and others. Methods for preparation of these compositions are known to those skilled in the art. The contemplated compositions may contain 0.001%-100%

20 active ingredient, preferably 0.1-85%, typically 75-95%.

The active compounds or pharmaceutically acceptable derivatives may be prepared with carriers that protect the compound against rapid elimination from the body, such as time release formulations or coatings. The compositions may include other active compounds to obtain desired

25 combinations of properties. The compounds provided herein, or pharmaceutically acceptable derivatives thereof as described herein, may also be advantageously administered for therapeutic or prophylactic purposes together with another pharmacological agent known in the general art to be of value in treating one or more of the diseases or medical conditions referred to

30 hereinabove, such as diseases or disorders associated with nuclear receptor activity or in which nuclear receptor activity is implicated. It is to be

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understood that such combination therapy constitutes a further aspect of the compositions and methods of treatment provided herein.

### 1. Compositions for oral administration

Oral pharmaceutical dosage forms are either solid, gel or liquid. The  
5 solid dosage forms are tablets, capsules, granules, and bulk powders. Types of oral tablets include compressed, chewable lozenges and tablets which may be enteric-coated, sugar-coated or film-coated. Capsules may be hard or soft gelatin capsules, while granules and powders may be provided in  
10 non-effervescent or effervescent form with the combination of other ingredients known to those skilled in the art.

In certain embodiments, the formulations are solid dosage forms, preferably capsules or tablets. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder; a diluent; a disintegrating agent; a lubricant; a glidant; a  
15 sweetening agent; and a flavoring agent.

Examples of binders include microcrystalline cellulose, gum tragacanth, glucose solution, acacia mucilage, gelatin solution, sucrose and starch paste. Lubricants include talc, starch, magnesium or calcium stearate, lycopodium and stearic acid. Diluents include, for example, lactose, sucrose,  
20 starch, kaolin, salt, mannitol and dicalcium phosphate. Glidants include, but are not limited to, colloidal silicon dioxide. Disintegrating agents include crosscarmellose sodium, sodium starch glycolate, alginic acid, corn starch, potato starch, bentonite, methylcellulose, agar and carboxymethylcellulose. Coloring agents include, for example, any of the approved certified water  
25 soluble FD and C dyes, mixtures thereof; and water insoluble FD and C dyes suspended on alumina hydrate. Sweetening agents include sucrose, lactose, mannitol and artificial sweetening agents such as saccharin, and any number of spray dried flavors. Flavoring agents include natural flavors extracted from plants such as fruits and synthetic blends of compounds which produce a  
30 pleasant sensation, such as, but not limited to peppermint and methyl salicylate. Wetting agents include propylene glycol monostearate, sorbitan

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monooleate, diethylene glycol monolaurate and polyoxyethylene laural ether. Emetic-coatings include fatty acids, fats, waxes, shellac, ammoniated shellac and cellulose acetate phthalates. Film coatings include hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000 and cellulose

5 acetate phthalate.

If oral administration is desired, the compound could be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity in the stomach and releases the active compound in the  
10 intestine. The composition may also be formulated in combination with an antacid or other such ingredient.

When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the  
15 physical form of the dosage unit, for example, coatings of sugar and other enteric agents. The compounds can also be administered as a component of an elixir, suspension, syrup, wafer, sprinkle, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

20 The active materials can also be mixed with other active materials which do not impair the desired action, or with materials that supplement the desired action, such as antacids, H<sub>2</sub> blockers, and diuretics. The active ingredient is a compound or pharmaceutically acceptable derivative thereof as described herein. Higher concentrations, up to about 98% by weight of the  
25 active ingredient may be included.

Pharmaceutically acceptable carriers included in tablets are binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, and wetting agents. Enteric-coated tablets, because of the enteric-coating, resist the action of stomach acid and dissolve or  
30 disintegrate in the neutral or alkaline intestines. Sugar-coated tablets are compressed tablets to which different layers of pharmaceutically

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- acceptable substances are applied. Film-coated tablets are compressed tablets which have been coated with a polymer or other suitable coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle utilizing the pharmaceutically acceptable
- 5 substances previously mentioned. Coloring agents may also be used in the above dosage forms. Flavoring and sweetening agents are used in compressed tablets, sugar-coated, multiple compressed and chewable tablets. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.
- 10 Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Aqueous solutions include, for example, elixirs and syrups. Emulsions are either oil-in-water or water-in-oil.
- 15 Elixirs are clear, sweetened, hydroalcoholic preparations. Pharmaceutically acceptable carriers used in elixirs include solvents. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may contain a preservative. An emulsion is a two-phase system in which one liquid is dispersed in the form of small globules throughout another liquid.
- 20 Pharmaceutically acceptable carriers used in emulsions are non-aqueous liquids, emulsifying agents and preservatives. Suspensions use pharmaceutically acceptable suspending agents and preservatives. Pharmaceutically acceptable substances used in non-effervescent granules, to be reconstituted into a liquid oral dosage form, include diluents, sweeteners
- 25 and wetting agents. Pharmaceutically acceptable substances used in effervescent granules, to be reconstituted into a liquid oral dosage form, include organic acids and a source of carbon dioxide. Coloring and flavoring agents are used in all of the above dosage forms.
- Solvents include glycerin, sorbitol, ethyl alcohol and syrup. Examples
- 30 of preservatives include glycerin, methyl and propylparaben, benzoic acid, sodium benzoate and alcohol. Examples of non-aqueous liquids utilized in

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emulsions include mineral oil and cottonseed oil. Examples of emulsifying agents include gelatin, acacia, tragacanth, bentonite, and surfactants such as polyoxyethylene sorbitan monooleate. Suspending agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum and acacia. Diluents  
5 include lactose and sucrose. Sweetening agents include sucrose, syrups, glycerin and artificial sweetening agents such as saccharin. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene lauryl ether. Organic adds include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate  
10 and sodium carbonate. Coloring agents include any of the approved certified water soluble FD and C dyes, and mixtures thereof. Flavoring agents include natural flavors extracted from plants such fruits, and synthetic blends of compounds which produce a pleasant taste sensation.

For a solid dosage form, the solution or suspension, in for example  
15 propylene carbonate, vegetable oils or triglycerides, is preferably encapsulated in a gelatin capsule. Such solutions, and the preparation and encapsulation thereof, are disclosed in U.S. Patent Nos 4,328,245; 4,409,239; and 4,410,545. For a liquid dosage form, the solution, *e.g.*, for example, in a polyethylene glycol, may be diluted with a sufficient quantity of a  
20 pharmaceutically acceptable liquid carrier, *e.g.*, water, to be easily measured for administration.

Alternatively, liquid or semi-solid oral formulations may be prepared by dissolving or dispersing the active compound or salt in vegetable oils, glycols, triglycerides, propylene glycol esters (*e.g.*, propylene carbonate) and other  
25 such carriers, and encapsulating these solutions or suspensions in hard or soft gelatin capsule shells. Other useful formulations include those set forth in U.S. Patent Nos. Re 28,819 and 4,358,603. Briefly, such formulations include, but are not limited to, those containing a compound provided herein, a dialkylated mono- or poly-alkylene glycol, including, but not limited to, 1,2-  
30 dimethoxymethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-

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750-dimethyl ether wherein 350, 550 and 750 refer to the approximate average molecular weight of the polyethylene glycol, and one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone,

- 5 hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, thiodipropionic acid and its esters, and dithiocarbamates.

- Other formulations include, but are not limited to, aqueous alcoholic solutions including a pharmaceutically acceptable acetal. Alcohols used in
- 10 these formulations are any pharmaceutically acceptable water-miscible solvents having one or more hydroxyl groups, including, but not limited to, propylene glycol and ethanol. Acetals include, but are not limited to, di(lower alkyl) acetals of lower alkyl aldehydes such as acetaldehyde diethyl acetal.

- In all embodiments, tablets and capsules formulations may be coated
- 15 as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient. Thus, for example, they may be coated with a conventional enterically digestible coating, such as phenylsalicylate, waxes and cellulose acetate phthalate.

## 2. Injectables, solutions and emulsions

- 20 Parenteral administration, generally characterized by injection, either subcutaneously, intramuscularly or intravenously is also contemplated herein. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline,
- 25 dextrose, glycerol or ethanol. In addition, if desired, the pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, stabilizers, solubility enhancers, and other such agents, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate and
- 30 cyclodextrins. Implantation of a slow-release or sustained-release system, such that a constant level of dosage is maintained (see, e.g., U.S. Patent No.

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3,710,795) is also contemplated herein. Briefly, a compound provided herein is dispersed in a solid inner matrix, e.g., polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol and cross-linked partially hydrolyzed polyvinyl acetate, that is surrounded by an outer polymeric membrane, e.g., polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, that is insoluble in body fluids. The compound diffuses through the outer polymeric membrane in a release rate controlling step. The percentage of active compound contained in such parenteral compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the subject.

Parenteral administration of the compositions includes intravenous, subcutaneous and intramuscular administrations. Preparations for parenteral administration include sterile solutions ready for injection, sterile dry soluble products, such as lyophilized powders, ready to be combined with a solvent just prior to use, including hypodermic tablets, sterile suspensions ready for injection, sterile dry insoluble products ready to be combined with a vehicle just prior to use and sterile emulsions. The solutions may be either aqueous or nonaqueous.

If administered intravenously, suitable carriers include physiological saline or phosphate buffered saline (PBS), and solutions containing thickening

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and solubilizing agents, such as glucose, polyethylene glycol, and polypropylene glycol and mixtures thereof.

Pharmaceutically acceptable carriers used in parenteral preparations include aqueous vehicles, nonaqueous vehicles, antimicrobial agents, 5 isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents and other pharmaceutically acceptable substances.

- Examples of aqueous vehicles include Sodium Chloride Injection, Ringers Injection, Isotonic Dextrose Injection, Sterile Water Injection, 10 Dextrose and Lactated Ringers Injection. Nonaqueous parenteral vehicles include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil and peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations must be added to parenteral preparations packaged in multiple-dose containers which include phenols or cresols, mercurials, benzyl alcohol, 15 chlorobutanol, methyl and propyl p-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride and benzethonium chloride. Isotonic agents include sodium chloride and dextrose. Buffers include phosphate and citrate. Antioxidants include sodium bisulfate. Local anesthetics include procaine hydrochloride. Suspending and dispersing agents include sodium 20 carboxymethylcellulose, hydroxypropyl methylcellulose and polyvinylpyrrolidone. Emulsifying agents include Polysorbate 80 (TWEEN® 80). A sequestering or chelating agent of metal ions include EDTA. Pharmaceutical carriers also include ethyl alcohol, polyethylene glycol and propylene glycol for water miscible vehicles and sodium hydroxide, 25 hydrochloric acid, citric acid or lactic acid for pH adjustment.

The concentration of the pharmaceutically active compound is adjusted so that an injection provides an effective amount to produce the desired pharmacological effect. The exact dose depends on the age, weight and condition of the patient or animal as is known in the art.



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The unit-dose parenteral preparations are packaged in an ampoule, a vial or a syringe with a needle. All preparations for parenteral administration must be sterile, as is known and practiced in the art.

- Illustratively, intravenous or intraarterial infusion of a sterile aqueous
- 5 solution containing an active compound is an effective mode of administration. Another embodiment is a sterile aqueous or oily solution or suspension containing an active material injected as necessary to produce the desired pharmacological effect.

- Injectables are designed for local and systemic administration.
- 10 Typically a therapeutically effective dosage is formulated to contain a concentration of at least about 0.1% w/w up to about 90% w/w or more, preferably more than 1% w/w of the active compound to the treated tissue(s). The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is
- 15 understood that the precise dosage and duration of treatment is a function of the tissue being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and dosage values may also vary with the age of the individual treated. It is to be further understood that for any particular
- 20 subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed formulations.
- 25 The compound may be suspended in micronized or other suitable form or may be derivatized to produce a more soluble active product or to produce a prodrug. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is
- 30 sufficient for ameliorating the symptoms of the condition and may be empirically determined.

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### 3. Lyophilized powders

Of interest herein are also lyophilized powders, which can be reconstituted for administration as solutions, emulsions and other mixtures. They may also be reconstituted and formulated as solids or gels.

- 5       The sterile, lyophilized powder is prepared by dissolving a compound provided herein, or a pharmaceutically acceptable derivative thereof, in a suitable solvent. The solvent may contain an excipient which improves the stability or other pharmacological component of the powder or reconstituted solution, prepared from the powder. Excipients that may be used include, but
- 10   are not limited to, dextrose, sorbitol, fructose, corn syrup, xylitol, glycerin, glucose, sucrose or other suitable agent. The solvent may also contain a buffer, such as citrate, sodium or potassium phosphate or other such buffer known to those of skill in the art at, typically, about neutral pH. Subsequent
- 15   sterile filtration of the solution followed by lyophilization under standard conditions known to those of skill in the art provides the desired formulation. Generally, the resulting solution will be apportioned into vials for lyophilization. Each vial will contain a single dosage (10-1000 mg, preferably 100-500 mg) or multiple dosages of the compound. The lyophilized powder can be stored under appropriate conditions, such as at about 4 °C to room temperature.
- 20       Reconstitution of this lyophilized powder with water for injection provides a formulation for use in parenteral administration. For reconstitution, about 1-50 mg, preferably 5-35 mg, more preferably about 9-30 mg of lyophilized powder, is added per mL of sterile water or other suitable carrier. The precise amount depends upon the selected compound. Such amount
- 25   can be empirically determined.

### 4. Topical administration

- Topical mixtures are prepared as described for the local and systemic administration. The resulting mixture may be a solution, suspension, emulsions or the like and are formulated as creams, gels, ointments,
- 30   emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, foams,

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aerosols, irrigations, sprays, suppositories, bandages, dermal patches or any other formulations suitable for topical administration.

The compounds or pharmaceutically acceptable derivatives thereof may be formulated as aerosols for topical application, such as by inhalation (see, e.g., U.S. Patent Nos. 4,044,126, 4,414,209, and 4,364,923, which describe aerosols for delivery of a steroid useful for treatment of inflammatory diseases, particularly asthma). These formulations for administration to the respiratory tract can be in the form of an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the formulation will typically have diameters of less than 50 microns, preferably less than 10 microns.

The compounds may be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye or for intracisternal or intraspinal application. Topical administration is contemplated for transdermal delivery and also for administration to the eyes or mucosa, or for inhalation therapies. Nasal solutions of the active compound alone or in combination with other pharmaceutically acceptable excipients can also be administered.

These solutions, particularly those intended for ophthalmic use, may be formulated as 0.01% - 10% isotonic solutions, pH about 5-7, with appropriate salts.

#### **5. Compositions for other routes of administration**

Other routes of administration, such as topical application, transdermal patches, and rectal administration are also contemplated herein.

For example, pharmaceutical dosage forms for rectal administration are rectal suppositories, capsules and tablets for systemic effect. Rectal suppositories are used herein mean solid bodies for insertion into the rectum which melt or soften at body temperature releasing one or more pharmacologically or therapeutically active ingredients. Pharmaceutically

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acceptable substances utilized in rectal suppositories are bases or vehicles and agents to raise the melting point. Examples of bases include cocoa butter (theobroma oil), glycerin-gelatin, carbowax (polyoxyethylene glycol) and appropriate mixtures of mono-, di- and triglycerides of fatty acids.

- 5 Combinations of the various bases may be used. Agents to raise the melting point of suppositories include spermaceti and wax. Rectal suppositories may be prepared either by the compressed method or by molding. The typical weight of a rectal suppository is about 2 to 3 gm.

- Tablets and capsules for rectal administration are manufactured using  
10 the same pharmaceutically acceptable substance and by the same methods as for formulations for oral administration.

#### 6. Articles of manufacture

- The compounds or pharmaceutically acceptable derivatives may be packaged as articles of manufacture containing packaging material, a  
15 compound or pharmaceutically acceptable derivative thereof provided herein, which is effective for modulating the activity of nuclear receptors, including FXR, LXR and/or orphan nuclear receptors, or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor, including FXR, LXR and/or orphan nuclear receptor, mediated diseases or disorders, or  
20 diseases or disorders in which nuclear receptor activity, including FXR, LXR and/or orphan nuclear receptor activity, is implicated, within the packaging material, and a label that indicates that the compound or composition, or pharmaceutically acceptable derivative thereof, is used for modulating the activity of nuclear receptors, including FXR, LXR and/or orphan nuclear  
25 receptors, or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor, including FXR, LXR and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including FXR, LXR and/or orphan nuclear receptor activity, is implicated.

- 30 The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products

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are well known to those of skill in the art. See, e.g., U.S. Patent Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. A wide array of formulations of the compounds and compositions provided herein are contemplated as are a variety of treatments for any disease or disorder in which nuclear receptor activity, including FXR, LXR and/or orphan nuclear receptor activity, is implicated as a mediator or contributor to the symptoms or cause.

#### **E. Evaluation of the Activity of the Compounds**

Standard physiological, pharmacological and biochemical procedures are available for testing the compounds to identify those that possess biological activities that modulate the activity of nuclear receptors, including the FXR. Such assays include, for example, biochemical assays such as binding assays, fluorescence polarization assays, FRET based coactivator recruitment assays (see generally Glickman *et al.*, *J. Biomolecular Screening*, 7 No. 1 3-10 (2002)), as well as cell based assays including the co-transfection assay, the use of LBD-Gal 4 chimeras and protein-protein interaction assays (see, Lehmann. *et al.*, *J. Biol Chem.*, 272(6) 3137-3140 (1997)).

High throughput screening systems are commercially available (see, e.g., Zymark Corp., Hopkinton, MA; Air Technical Industries, Mentor, OH; Beckman Instruments Inc., Fullerton, CA; Precision Systems, Inc., Natick, MA) that enable these assays to be run in a high throughput mode. These systems typically automate entire procedures, including all sample and reagent pipetting, liquid dispensing timed incubations, and final readings of the microplate in detector(s) appropriate for the assay. These configurable systems provide high throughput and rapid start up as well as a high degree of flexibility and customization. The manufacturers of such systems provide detailed protocols for various high throughput systems. Thus, for example,

Zymark Corp. provides technical bulletins describing screening systems for detecting the modulation of gene transcription, ligand binding, and the like.

Assays that do not require washing or liquid separation steps are preferred for such high throughput screening systems and include

5 biochemical assays such as fluorescence polarization assays (see for example, Owicki, J., *Biomol Screen* 2000 Oct;5(5):297) scintillation proximity assays (SPA) (see for example, Carpenter *et al.*, *Methods Mol Biol* 2002;190:31-49) and fluorescence resonance energy transfer energy transfer (FRET) or time resolved FRET based coactivator recruitment assays

10 (Mukherjee *et al.*, *J Steroid Biochem Mol Biol* 2002 Jul;81(3):217-25; (Zhou *et al.*, *Mol Endocrinol.* 1998 Oct;12(10):1594-604). Generally such assays can be preformed using either the full length receptor, or isolated ligand binding domain (LBD). In the case of FXR, the LBD comprises amino acids 244 to 472 of the full length sequence.

15 If a fluorescently labeled ligand is available, fluorescence polarization assays provide a way of detecting binding of compounds to the nuclear receptor of interest by measuring changes in fluorescence polarization that occur as a result of the displacement of a trace amount of the label ligand by the compound. Additionally this approach can also be used to monitor the

20 ligand dependent association of a fluorescently labeled coactivator peptide to the nuclear receptor of interest to detect ligand binding to the nuclear receptor of interest.

The ability of a compound to bind to a receptor, or heterodimer complex with RXR, can also be measured in a homogeneous assay format by

25 assessing the degree to which the compound can compete off a radiolabelled ligand with known affinity for the receptor using a scintillation proximity assay (SPA). In this approach, the radioactivity emitted by a radiolabelled compound generates an optical signal when it is brought into close proximity to a scintillant such as a Ysi-copper containing bead, to which the nuclear receptor

30 is bound. If the radiolabelled compound is displaced from the nuclear receptor the amount of light emitted from the nuclear receptor bound scintillant

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decreases, and this can be readily detected using standard microplate liquid scintillation plate readers such as, for example, a Wallac MicroBeta reader.

The heterodimerization of FXR with RXR $\alpha$  can also be measured by fluorescence resonance energy transfer (FRET), or time resolved FRET, to  
5 monitor the ability of the compounds provided herein to bind to FXR or other nuclear receptors. Both approaches rely upon the fact that energy transfer from a donor molecule to an acceptor molecule only occurs when donor and acceptor are in close proximity. Typically the purified LBD of the nuclear receptor of interest is labeled with biotin then mixed with stoichiometric  
10 amounts of europium labeled streptavidin (Wallac Inc.), and the purified LBD of RXR $\alpha$  is labeled with a suitable fluorophore such as CY5™. Equimolar amounts of each modified LBD are mixed together and allowed to equilibrate for at least 1 hour prior to addition to either variable or constant concentrations of the sample for which the affinity is to be determined. After  
15 equilibration, the time-resolved fluorescent signal is quantitated using a fluorescent plate reader. The affinity of the compound can then be estimated from a plot of fluorescence versus concentration of compound added.

This approach can also be exploited to measure the ligand dependent interaction of a co-activator peptide with a nuclear receptor in order to  
20 characterize the agonist or antagonist activity of the compounds disclosed herein. Typically the assay in this case involves the use a recombinant Glutathione-S-transferase (GST)-nuclear receptor ligand binding domain (LBD) fusion protein and a synthetic biotinylated peptide sequenced derived from the receptor interacting domain of a co-activator peptide such as the  
25 steroid receptor coactivator 1 (SRC-1). Typically GST-LBD is labeled with a europium chelate (donor) via a europium-tagged anti-GST antibody, and the coactivator peptide is labeled with allophycocyanin via a streptavidin-biotin linkage.

In the presence of an agonist for the nuclear receptor, the peptide is  
30 recruited to the GST-LBD bringing europium and allophycocyanin into close proximity to enable energy transfer from the europium chelate to the

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allophycocyanin. Upon excitation of the complex with light at 340 nm  
excitation energy absorbed by the europium chelate is transmitted to the  
allophycocyanin moiety resulting in emission at 665 nm. If the europium  
chelate is not brought in to close proximity to the allophycocyanin moiety there  
5 is little or no energy transfer and excitation of the europium chelate results in  
emission at 615 nm. Thus the intensity of light emitted at 665 nm gives an  
indication of the strength of the protein-protein interaction. The activity of a  
nuclear receptor antagonist can be measured by determining the ability of a  
compound to competitively inhibit (*i.e.*,  $IC_{50}$ ) the activity of an agonist for the  
10 nuclear receptor.

In addition a variety of cell based assay methodologies may be  
successfully used in screening assays to identify and profile the specificity of  
compounds of the present invention. These approaches include the co-  
transfection assay, translocation assays, complementation assays and the  
15 use of gene activation technologies to over express endogenous nuclear  
receptors.

Three basic variants of the co-transfection assay strategy exist, co-  
transfection assays using full-length nuclear receptor, co transfection assays  
using chimeric nuclear receptors comprising the ligand binding domain of the  
20 nuclear receptor of interest fused to a heterologous DNA binding domain, and  
assays based around the use of the mammalian two hybrid assay system.

The basic co-transfection assay is based on the co-transfection into the  
cell of an expression plasmid to express the nuclear receptor of interest in the  
cell with a reporter plasmid comprising a reporter gene whose expression is  
25 under the control of DNA sequence that is capable of interacting with that  
nuclear receptor. (See for example US Patents Nos. 5,071,773; 5,298,429  
and 6,416,957). Treatment of the transfected cells with an agonist for the  
nuclear receptor increases the transcriptional activity of that receptor which is  
reflected by an increase in expression of the reporter gene, which may be  
30 measured by a variety of standard procedures.



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For those receptors that function as heterodimers with RXR, such as FXR, the co-transfection assay typically includes the use of expression plasmids for both the nuclear receptor of interest and RXR. Typical co-transfection assays require access to the full length nuclear receptor and  
5 suitable response elements that provide sufficient screening sensitivity and specificity to the nuclear receptor of interest.

Genes encoding the following full-length previously described proteins, which are suitable for use in the co-transfection studies and profiling the compounds described herein, include rat FXR (SEQ ID NO. 5), human FXR  
10 (SEQ ID NO.7), human RXR  $\alpha$  (SEQ ID NO. 9), human RXR  $\beta$  (SEQ ID NO. 17), human RXR. $\gamma$  (SEQ ID NO. 15), human LXR  $\alpha$  (SEQ ID NO. 1), human LXR  $\beta$  (SEQ ID NO. 3), human PPAR $\alpha$  (SEQ ID NO. 11) and human PPAR  $\delta$  (SEQ ID NO. 13).

Reporter plasmids may be constructed using standard molecular  
15 biological techniques by placing cDNA encoding for the reporter gene downstream from a suitable minimal promoter. For example luciferase reporter plasmids may be constructed by placing cDNA encoding firefly luciferase immediately down stream from the herpes virus thymidine kinase promoter (located at nucleotides residues-105 to +51 of the thymidine kinase  
20 nucleotide sequence) which is linked in turn to the various response elements.

Numerous methods of co-transfecting the expression and reporter plasmids are known to those of skill in the art and may be used for the co-transfection assay to introduce the plasmids into a suitable cell type. Typically such a cell will not endogenously express nuclear receptors that interact with  
25 the response elements used in the reporter plasmid.

Numerous reporter gene systems are known in the art and include, for example, alkaline phosphatase Berger, J., *et al.* (1988) Gene 66 1-10; Kain, S.R. (1997) *Methods. Mol. Biol.* 63 49-60),  $\beta$ -galactosidase (See, U.S. Patent No. 5,070,012, issued Dec, 3, 1991 to Nolan *et al.*, and Bronstein, I., *et al.*,  
30 (1989) *J. Chemilum. Biolum.* 4 99-111), chloramphenicol acetyltransferase (See Gorman *et al.*, *Mol Cell Biol.* (1982) 2 1044-51),  $\beta$ -glucuronidase,

peroxidase,  $\beta$ -lactamase (U.S. Patent Nos. 5,741,657 and 5,955,604), catalytic antibodies, luciferases (U.S. Patents 5,221,623; 5,683,888; 5,674,713; 5,650,289; 5,843,746) and naturally fluorescent proteins (Tsien, R.Y. (1998) Annu. Rev. Biochem. 67 509-44).

- 5           The use of chimeras comprising the ligand binding domain (LBD) of the nuclear receptor of interest to a heterologous DNA binding domain (DBD) expands the versatility of cell based assays by directing activation of the nuclear receptor in question to defined DNA binding elements recognized by defined DNA binding domain (see WO95/18380). This assay expands the
- 10   utility of cell based co-transfection assays in cases where the biological response or screening window using the native DNA binding domain is not satisfactory.

- In general the methodology is similar to that used with the basic co-transfection assay, except that a chimeric construct is used in place of the full
- 15   length nuclear receptor. As with the full length nuclear receptor, treatment of the transfected cells with an agonist for the nuclear receptor LBD increases the transcriptional activity of the heterologous DNA binding domain which is reflected by an increase in expression of the reporter gene as described above. Typically for such chimeric constructs, the DNA binding domains from
- 20   defined nuclear receptors, or from yeast or bacterially derived transcriptional regulators such as members of the GAL 4 and Lex A / UmuD super families are used.

- A third cell based assay of utility for screening compounds of the present invention is a mammalian two-hybrid assay that measures the ability
- 25   of the nuclear hormone receptor to interact with a cofactor in the presence of a ligand. (See for example, US Patent Nos. US 5,667,973, 5,283,173 and 5,468,614). The basic approach is to create three plasmid constructs that enable the interaction of the nuclear receptor with the interacting protein to be coupled to a transcriptional readout within a living cell. The first construct is an
- 30   expression plasmid for expressing a fusion protein comprising the interacting protein, or a portion of that protein containing the interacting domain, fused to

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a GAL4 DNA binding domain. The second expression plasmid comprises DNA encoding the nuclear receptor of interest fused to a strong transcription activation domain such as VP16, and the third construct comprises the reporter plasmid comprising a reporter gene with a minimal promoter and

5 GAL4 upstream activating sequences.

Once all three plasmids are introduced into a cell, the GAL4 DNA binding domain encoded in the first construct allows for specific binding of the fusion protein to GAL4 sites upstream of a minimal promoter. However because the GAL4 DNA binding domain typically has no strong transcriptional

10 activation properties in isolation, expression of the reporter gene occurs only at a low level. In the presence of a ligand, the nuclear receptor-VP16 fusion protein can bind to the GAL4-interacting protein fusion protein bringing the strong transcriptional activator VP16 in close proximity to the GAL4 binding sites and minimal promoter region of the reporter gene. This interaction

15 significantly enhances the transcription of the reporter gene, which can be measured for various reporter genes as described above. Transcription of the reporter gene is thus driven by the interaction of the interacting protein and nuclear receptor of interest in a ligand dependent fashion.

Any compound which is a candidate for activation of FXR may be

20 tested by these methods. Generally, compounds are tested at several different concentrations to optimize the chances that activation of the receptor will be detected and recognized if present. Typically assays are performed in triplicate and vary within experimental error by less than 15%. Each experiment is typically repeated three or more times with similar results.

25 Activity of the reporter gene can be conveniently normalized to the internal control and the data plotted as fold activation relative to untreated cells. A positive control compound (agonist) may be included along with DMSO as high and low controls for normalization of the assay data. Similarly, antagonist activity can be measured by determining the ability of a compound

30 to competitively inhibit the activity of an agonist.

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Additionally the compounds and compositions can be evaluated for their ability to increase or decrease the expression of genes known to be modulated by FXR and other nuclear receptors *in vivo*, using Northern-blot, RT PCR or oligonucleotide microarray analysis to analyze RNA levels.

- 5 Western-blot analysis can be used to measure expression of proteins encoded by FXR target genes. Genes that are known to be regulated by the FXR include cholesterol 7  $\alpha$ -hydroxylase (CYP7A1), the rate limiting enzyme in the conversion of cholesterol to bile acids, the small heterodimer partner-1 (SHP-1), the bile salt export pump (BSEP, ABCB11), canalicular bile acid  
10 export protein, sodium taurocholate cotransporting polypeptide (NTCP, SLC10A1) and intestinal bile acid binding protein (I-BABP).

Established animal models exist for a number of diseases of direct relevance to the claimed compounds and these can be used to further profile and characterize the claimed compounds. These model systems include

- 15 diabetic dislipidemia using Zucker (fa/fa) rats or (db/db) mice, spontaneous hyperlipidemia using apolipoprotein E deficient mice (ApoE<sup>-/-</sup>), diet-induced hyperlipidemia, using low density lipoprotein receptor deficient mice (LDLR<sup>-/-</sup>) and atherosclerosis using both the Apo E<sup>-/-</sup> and LDL<sup>-/-</sup> mice fed a western diet. (21% fat, 0.05% cholesterol). Additionally FXR or LXR animal models  
20 (e.g., knockout mice) can be used to further evaluate the present compounds and compositions *in vivo* (see, for example, Sinal, *et al.*, *Cell*, 102: 731-744 (2000), Peet, *et al.*, *Cell*, 93:693-704 (1998)).

#### F. Methods of use of the compounds and compositions

Methods of use of the compounds and compositions provided herein

- 25 are also provided. The methods involve both *in vitro* and *in vivo* uses of the compounds and compositions for altering nuclear receptor activity, including FXR, LXR and/or orphan nuclear receptor activity, and for treatment, prevention, or amelioration of one or more symptoms of diseases or disorder that are modulated by nuclear receptor activity, including FXR, LXR and/or  
30 orphan nuclear receptor activity, or in which nuclear receptor activity, including FXR, LXR and/or orphan nuclear receptor activity, is implicated.

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Methods of reducing cholesterol levels and of modulating cholesterol metabolism are provided. As described above, FXR is implicated in modulating cholesterol metabolism, catabolism and absorption of dietary cholesterol. See, e.g., International Patent Application Publication No.

5 00/40965.

Method of altering nuclear receptor activity, including FXR, LXR and/or orphan nuclear receptor activity, by contacting the receptor with one or more compounds or compositions provided herein, are provided.

10 Methods of treatment, prevention, or amelioration of one or more symptoms of a disease or disorder which is affected by cholesterol, triglyceride, or bile acid levels are provided.

15 Methods of treatment, prevention, or amelioration of one or more symptoms of hypercholesterolemia (see, e.g., International Patent Application Publication No. WO 00/57915); hyperlipoproteinemia (see, e.g., International Patent Application Publication No. WO 01/60818); hypertriglyceridemia, lipodystrophy, hyperglycemia or diabetes mellitus (see, e.g., International Patent Application Publication No. WO 01/82917); dyslipidemia, obesity, atherosclerosis, lipid disorders, cardiovascular disorders, or gallstone disease (see, e.g., International Patent Application Publication No. WO 00/37077);  
20 acne vulgaris or acneiform skin conditions (see, e.g., International Patent Application Publication No. WO 00/49992); atherosclerosis, diabetes, Parkinson's disease, inflammation, immunological disorders, obesity, cancer or Alzheimer's disease (see, e.g., International Patent Application Publication No. WO 00/17334); conditions characterized by a perturbed epidermal barrier  
25 function, hyperlipidemia, cholestasis, peripheral occlusive disease, ischemic stroke, or conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane (see, e.g., U.S. Patent Nos. 6,184,215 and 6,187,814, and International Patent Application Publication No. WO 98/32444) are provided.

Methods of increasing cholesterol efflux from mammalian cells using the compounds and compositions provided herein are provided (see, *e.g.*, International Patent Application Publication No. WO 00/78972).

Methods of increasing the expression of ATP-Binding Cassette (ABC1)

- 5 in mammalian cells using the compounds and compositions provided herein are provided (see, *e.g.*, International Patent Application Publication No. WO 00/78972).

- Further provided herein are methods for the treatment, prevention, or amelioration of one or more symptoms of cholestasis, as well as treating the  
10 complications of cholestasis by administering a compound provided herein.

Cholestasis is typically caused by factors within the liver (intrahepatic) or outside the liver (extrahepatic) and leads to the accumulation of bile salts, bile pigment bilirubin, and lipids in the blood stream instead of being eliminated normally.

- 15 Intrahepatic cholestasis is characterized by widespread blockage of small ducts or by disorders, such as hepatitis, that impair the body's ability to eliminate bile. Intrahepatic cholestasis may also be caused by alcoholic liver disease, primary biliary cirrhosis, cancer that has spread (metastasized) from another part of the body, primary sclerosing cholangitis, gallstones, biliary  
20 colic and acute cholecystitis. It can also occur as a complication of surgery, serious injury, infection, or intravenous feeding or be drug induced. Cholestasis may also occur as a complication of pregnancy and often develops during the second and third trimesters.

- Extrahepatic cholestasis is most often caused by choledocholithiasis  
25 (Bile Duct Stones), benign biliary strictures (non-cancerous narrowing of the common duct), cholangiocarcinoma (ductal carcinoma) and pancreatic carcinoma. Extrahepatic cholestasis can occur as a side effect of many medications.

- Accordingly, compounds provided herein may be used for the  
30 treatment, prevention, or amelioration of one or more symptoms of intrahepatic or extrahepatic cholestasis, including without limitation, biliary

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artesia, obstetric cholestasis, neonatal cholestasis, drug induced cholestasis, cholestasis arising from Hepatitis C infection, chronic cholestatic liver disease such as primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC).

- 5           Methods of treating, preventing, or ameliorating one or more symptoms of hypocholesterolemia using the compounds and compositions provided herein are also provided.

**G.    Combination Therapy**

- Also contemplated herein is combination therapy using a compound
- 10   provided herein, or a pharmaceutically acceptable derivative thereof, in combination with one or more of the following: antihyperlipidemic agents, plasma HDL-raising agents, antihypercholesterolemic agents, cholesterol biosynthesis inhibitors (such as HMG CoA reductase inhibitors, such as lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and rivastatin),
- 15   acyl-coenzyme A:cholesterol acyltransferase (ACAT) inhibitors, probucol, raloxifene, nicotinic acid, niacinamide, cholesterol absorption inhibitors, bile acid sequestrants (such as anion exchange resins, or quaternary amines (e.g., cholestyramine or colestipol)), low density lipoprotein receptor inducers, clofibrate, fenofibrate, benzofibrate, ciprofibrate, gemfibrozil, vitamin B<sub>6</sub>,
- 20   vitamin B<sub>12</sub>, anti-oxidant vitamins,  $\beta$ -blockers, anti-diabetes agents, angiotensin II antagonists, angiotensin converting enzyme inhibitors, platelet aggregation inhibitors, fibrinogen receptor antagonists, aspirin or fibric acid derivatives. The compound provided herein, or pharmaceutically acceptable derivative thereof, is administered simultaneously with, prior to, or after
- 25   administration of one or more of the above agents. Pharmaceutical compositions containing a compound provided herein and one or more of the above agents are also provided.

- Combination therapy includes administration of a single pharmaceutical dosage formulation which contains a FXR selective compound and one or
- 30   more additional active agents, as well as administration of the FXR selective compound and each active agent in its own separate pharmaceutical dosage

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Dosage information for HMG-CoA reductase inhibitors is well known in the art, since several HMG-CoA reductase inhibitors are marketed in the U.S. In particular, the daily dosage amounts of the HMG-CoA reductase inhibitor may be the same or similar to those amounts which are employed for anti-  
5 hypercholesterolemic treatment and which are described in the *Physicians' Desk Reference* (PDR). For example, see the 50th Ed. of the PDR, 1996 (Medical Economics Co); in particular, see at page 216 the heading "Hypolipidemics," sub-heading "HMG-CoA Reductase Inhibitors," and the reference pages cited therein. Preferably, the oral dosage amount of HMG-  
10 CoA reductase inhibitor is from about 1 to 200 mg/day and, more preferably, from about 5 to 160 mg/day. However, dosage amounts will vary depending on the potency of the specific HMG-CoA reductase inhibitor used as well as other factors as noted above. An HMG-CoA reductase inhibitor which has sufficiently greater potency may be given in sub-milligram daily dosages.  
15 As examples, the daily dosage amount for simvastatin may be selected from 5 mg, 10 mg, 20 mg, 40 mg, 80 mg and 160 mg for lovastatin, 10 mg, 20 mg, 40 mg and 80 mg; for fluvastatin sodium, 20 mg, 40 mg and 80 mg; and for pravastatin sodium, 10 mg, 20 mg, and 40 mg. The daily dosage amount for atorvastatin calcium may be in the range of from 1 mg to 160 mg and,  
20 more particularly, from 5 mg to 80 mg. Oral administration may be in a single or divided doses of two, three, or four times daily, although a single daily dose of the HMG-CoA reductase inhibitor is preferred.

The compounds of the present invention can be utilized in methods for decreasing hyperglycemia and insulin resistance or for methods of treating  
25 type II diabetes. The compounds can be identified, formulated, and administered as described above.

Diabetes mellitus, commonly called diabetes, refers to a disease process derived from multiple causative factors and characterized by elevated levels of plasma glucose, referred to as hyperglycemia. See, e.g., LeRoith, D.  
30 et al., (eds.), DIABETES MELLITUS (Lippincott-Raven Publishers, Philadelphia, Pa. U.S.A. 1996). According to the American Diabetes



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Association, diabetes mellitus is estimated to affect approximately 6% of the world population. Uncontrolled hyperglycemia is associated with increased and premature mortality due to an increased risk for macrovascular and macrovascular diseases, including nephropathy, neuropathy, retinopathy,

5 hypertension, cerebrovascular disease and coronary heart disease.

Therefore, control of glucose homeostasis is a critically important approach for the treatment of diabetes.

There are two major forms of diabetes: type 1 diabetes (formerly referred to as insulin-dependent diabetes or IDDM); and type 2 diabetes

10 (formerly referred to as noninsulin dependent diabetes or NIDDM).

Type 2 diabetes is a disease characterized by insulin resistance accompanied by relative, rather than absolute, insulin deficiency. Type 2 diabetes can range from predominant insulin resistance with relative insulin deficiency to predominant insulin deficiency with some insulin resistance.

15 Insulin resistance is the diminished ability of insulin to exert its biological action across a broad range of concentrations. In insulin resistant individuals, the body secretes abnormally high amounts of insulin to compensate for this defect. When inadequate amounts of insulin are present to compensate for insulin resistance and adequate control of glucose, a state of impaired  
20 glucose tolerance develops. In a significant number of individuals, insulin secretion declines further and the plasma glucose level rises, resulting in the clinical state of diabetes. Type 2 diabetes can be due to a profound resistance to insulin stimulating regulatory effects on glucose and lipid metabolism in the main insulin-sensitive tissues: muscle, liver and adipose tissue. This  
25 resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in liver. In Type 2 diabetes, free fatty acid levels are often elevated in obese and some non-obese patients and lipid oxidation is increased.

30 Premature development of atherosclerosis and increased rate of cardiovascular and peripheral vascular diseases are characteristic features of

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patients with diabetes. Hyperlipidemia is an important precipitating factor for these diseases. Hyperlipidemia is a condition generally characterized by an abnormal increase in serum lipids in the bloodstream and is an important risk factor in developing atherosclerosis and heart disease. For a review of disorders of lipid metabolism, see, e.g., Wilson, J. et al., (ed.), Disorders of Lipid Metabolism, Chapter 23, Textbook of Endocrinology, 9th Edition, (W. B. Sanders Company, Philadelphia, Pa. U.S.A. 1998). Hyperlipidemia is usually classified as primary or secondary hyperlipidemia. Primary hyperlipidemia is generally caused by genetic defects, while secondary hyperlipidemia is generally caused by other factors, such as various disease states, drugs, and dietary factors. Alternatively, hyperlipidemia can result from both a combination of primary and secondary causes of hyperlipidemia. Elevated cholesterol levels are associated with a number of disease states, including coronary artery disease, angina pectoris, carotid artery disease, strokes, cerebral arteriosclerosis, and xanthoma.

Dyslipidemia, or abnormal levels of lipoproteins in blood plasma, is a frequent occurrence among diabetics, and has been shown to be one of the main contributors to the increased incidence of coronary events and deaths among diabetic subjects (see, e.g., Joslin, E. Ann. Chim. Med. (1927) 5: 1061-1079). Epidemiological studies since then have confirmed the association and have shown a several-fold increase in coronary deaths among diabetic subjects when compared with nondiabetic subjects (see, e.g., Garcia, M. J. et al., Diabetes (1974) 23: 105-11 (1974); and Laakso, M. and Lehto, S., Diabetes Reviews (1997) 5(4): 294-315). Several lipoprotein abnormalities have been described among diabetic subjects (Howard B., et al., Arteriosclerosis (1978) 30: 153-162).

The term "insulin resistance" can be defined generally as a disorder of glucose metabolism. More specifically, insulin resistance can be defined as the diminished ability of insulin to exert its biological action across a broad range of concentrations producing less than the expected biologic effect. (see, e.g., Reaven, G. M., J. Basic & Clin. Phys. & Pharm. (1998) 9: 387-406 and

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- Flier, J. Ann Rev. Med. (1983) 34:145-60). Insulin resistant persons have a diminished ability to properly metabolize glucose and respond poorly, if at all, to insulin therapy. Manifestations of insulin resistance include insufficient insulin activation of glucose uptake, oxidation and storage in muscle and
- 5 inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in liver. Insulin resistance can cause or contribute to polycystic ovarian syndrome, Impaired Glucose Tolerance (IGT), gestational diabetes, hypertension, obesity, atherosclerosis and a variety of other disorders. Eventually, the insulin resistant individuals can progress to a point
- 10 where a diabetic state is reached. The association of insulin resistance with glucose intolerance, an increase in plasma triglyceride and a decrease in high-density lipoprotein cholesterol concentrations, high blood pressure, hyperuricemia, smaller denser low-density lipoprotein particles, and higher circulating levels of plasminogen activator inhibitor-1), has been referred to as
- 15 "Syndrome X" (see, e.g., Reaven, G. M., Physiol. Rev. (1995) 75: 473-486).

- The term "diabetes mellitus" or "diabetes" means a disease or condition that is generally characterized by metabolic defects in production and utilization of glucose which result in the failure to maintain appropriate blood sugar levels in the body. The result of these defects is elevated blood
- 20 glucose, referred to as "hyperglycemia." Type 2 diabetes often occurs in the face of normal, or even elevated, levels of insulin and can result from the inability of tissues to respond appropriately to insulin. Most type 2 diabetic patients are insulin resistant and have a relative deficiency of insulin, in that insulin secretion can not compensate for the resistance of peripheral tissues
- 25 to respond to insulin. In addition, many type 2 diabetics are obese. Other types of disorders of glucose homeostasis include Impaired Glucose Tolerance, which is a metabolic stage intermediate between normal glucose homeostasis and diabetes, and Gestational Diabetes Mellitus, which is glucose intolerance in pregnancy in women with no previous history of type 1
- 30 or type 2 diabetes.

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- The term "complication" of diabetes includes, but is not limited to, microvascular complications and macrovascular complications. Microvascular complications are those complications which generally result in small blood vessel damage. These complications include, e.g., retinopathy (the
- 5 impairment or loss of vision due to blood vessel damage in the eyes); neuropathy (nerve damage and foot problems due to blood vessel damage to the nervous system); and nephropathy (kidney disease due to blood vessel damage in the kidneys). macrovascular complications are those complications which generally result from large blood vessel damage. These
- 10 complications include, e.g., cardiovascular disease and peripheral vascular disease. Cardiovascular disease refers to diseases of blood vessels of the heart. See, e.g., Kaplan, R. M., et al., "Cardiovascular diseases" in HEALTH AND HUMAN BEHAVIOR, pp. 206-242 (McGraw-Hill, New York 1993). Cardiovascular disease is generally one of several forms, including, e.g.,
- 15 hypertension (also referred to as high blood pressure), coronary heart disease, stroke, and rheumatic heart disease. Peripheral vascular disease refers to diseases of any of the blood vessels outside of the heart. It is often a narrowing of the blood vessels that carry blood to leg and arm muscles.
- The term "hyperlipidemia" refers to the presence of an abnormally
- 20 elevated level of lipids in the blood. Hyperlipidemia can appear in at least three forms: (1) hypercholesterolemia, i.e., an elevated cholesterol level; (2) hypertriglyceridemia, i.e., an elevated triglyceride level; and (3) combined hyperlipidemia, i.e., a combination of hypercholesterolemia and hypertriglyceridemia.
- 25 The term "cholesterol" refers to a steroid alcohol that is an essential component of cell membranes and myelin sheaths and, as used herein, incorporates its common usage. Cholesterol also serves as a precursor for steroid hormones and bile acids.
- The term "triglyceride(s)" ("TGs"), as used herein, incorporates its
- 30 common usage. TGs consist of three fatty acid molecules esterified to a

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glycerol molecule and serve to store fatty acids which are used by muscle cells for energy production or are taken up and stored in adipose tissue.

The term "dyslipidemia" refers to abnormal levels of lipoproteins in blood plasma including both depressed and/or elevated levels of lipoproteins (e.g., elevated levels of LDL, VLDL and depressed levels of HDL).

Exemplary Primary Hyperlipidemia include, but are not limited to, the following: (1) Familial Hyperchylomicronemia, a rare genetic disorder which causes a deficiency in an enzyme, LP lipase, that breaks down fat molecules. The LP lipase deficiency can cause the accumulation of large quantities of fat or lipoproteins in the blood;

(2) Familial Hypercholesterolemia, a relatively common genetic disorder caused where the underlying defect is a series of mutations in the LDL receptor gene that result in malfunctioning LDL receptors and/or absence of the LDL receptors. This brings about ineffective clearance of LDL by the LDL receptors resulting in elevated LDL and total cholesterol levels in the plasma;

(3) Familial Combined Hyperlipidemia, also known as multiple lipoprotein-type hyperlipidemia; an inherited disorder where patients and their affected first-degree relatives can at various times manifest high cholesterol and high triglycerides. Levels of HDL cholesterol are often moderately decreased;

(4) Familial Defective Apolipoprotein B-100 is a relatively common autosomal dominant genetic abnormality. The defect is caused by a single nucleotide mutation that produces a substitution of glutamine for arginine which can cause reduced affinity of LDL particles for the LDL receptor. Consequently, this can cause high plasma LDL and total cholesterol levels;

(5) Familial Dysbetalipoproteinemia, also referred to as Type III Hyperlipoproteinemia, is an uncommon inherited disorder resulting in moderate to severe elevations of serum TG and cholesterol levels with abnormal apolipoprotein E function. HDL levels are usually normal; and

(6) Familial Hypertriglyceridemia, is a common inherited disorder in

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which the concentration of plasma VLDL is elevated. This can cause mild to moderately elevated triglyceride levels (and usually not cholesterol levels) and can often be associated with low plasma HDL levels.

Risk factors in exemplary Secondary Hyperlipidemia include, but are not limited to, the following: (1) disease risk factors, such as a history of type 1 diabetes, type 2 diabetes, Cushing's syndrome, hypothyroidism and certain types of renal failure; (2) drug risk factors, which include, birth control pills; hormones, such as estrogen, and corticosteroids; certain diuretics; and various .beta. blockers; (3) dietary risk factors include dietary fat intake per total calories greater than 40%; saturated fat intake per total calories greater than 10%; cholesterol intake greater than 300 mg per day; habitual and excessive alcohol use; and obesity; and (4) non-genetic dyslipidemias.

The methods of the present invention can be used effectively in combination with one or more additional active diabetes agents depending on the desired target therapy (see, e.g., Turner, N. et al. Prog. Drug Res. (1998) 51: 33-94; Haffner, S. Diabetes Care (1998) 21: 160-178; and DeFronzo, R. et al. (eds.), Diabetes Reviews (1997) Vol. 5 No. 4). A number of studies have investigated the benefits of combination therapies with oral agents (see, e.g., Mahler, R., J. Clin. Endocrinol. Metab. (1999) 84: 1165-71; United Kingdom Prospective Diabetes Study Group: UKPDS 28, Diabetes Care (1998) 21: 87-92; Bardin, C. W.,(ed.), CURRENT THERAPY IN ENDOCRINOLOGY AND METABOLISM, 6th Edition (Mosby-Year Book, Inc., St. Louis, Mo. 1997); Chiasson, J. et al., Ann. Intern. Med. (1994) 121: 928-935; Coniff, R. et al., Clin. Ther. (1997) 19: 16-26; Coniff, R. et al., Am. J. Med. (1995) 98: 443-451; and Iwamoto, Y. et al, Diabet. Med. (1996) 13 365-370; Kwiterovich, P. Am. J. Cardiol (1998) 82(12A): 3U-17U). These studies indicate that diabetes and hyperlipidemia modulation can be further improved by the addition of a second agent to the therapeutic regimen.

An example of combination therapy that modulates (prevents the onset of the symptoms or complications associated) atherosclerosis, is administered with one or more of the following active agents: an antihyperlipidemic agent; a

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- plasma HDL-raising agent; an antihypercholesterolemic agent, such as a cholesterol biosynthesis inhibitor, e.g., an hydroxymethylglutaryl (HMG) CoA reductase inhibitor (also referred to as statins, such as lovastatin, simvastatin, pravastatin, fluvastatin, and atorvastatin), an HMG-CoA synthase inhibitor, a
- 5 squalene epoxidase inhibitor, or a squalene synthetase inhibitor (also known as squalene synthase inhibitor); an acyl-coenzyme A cholesterol acyltransferase (ACAT) inhibitor, such as melinamide; probucol; nicotinic acid and the salts thereof and niacinamide; a cholesterol absorption inhibitor, such as  $\beta$ -sitosterol; a bile acid sequestrant anion exchange resin, such as
- 10 cholestyramine, colestipol or dialkylaminoalkyl derivatives of a cross-linked dextran; an LDL (low density lipoprotein) receptor inducer; fibrates, such as clofibrate, bezafibrate, fenofibrate, and gemfibrozil; vitamin B<sub>6</sub> (also known as pyridoxine) and the pharmaceutically acceptable salts thereof, such as the HCl salt; vitamin B<sub>12</sub> (also known as cyanocobalamin); vitamin B<sub>3</sub> (also known
- 15 as nicotinic acid and niacinamide, supra); anti-oxidant vitamins, such as vitamin C and E and beta carotene; a beta-blocker; an angiotensin II antagonist; an angiotensin converting enzyme inhibitor; and a platelet aggregation inhibitor, such as fibrinogen receptor antagonists (i.e., glycoprotein IIb/IIIa fibrinogen receptor antagonists) and aspirin.
- 20 Still another example of combination therapy can be seen in modulating diabetes (or treating diabetes and its related symptoms, complications, and disorders) with, for example, sulfonylureas (such as chlorpropamide, tolbutamide, acetohexamide, tolazamide, glyburide, gliclazide, glynase, glimepiride, and glipizide), biguanides (such as
- 25 metformin), thiazolidinediones (such as ciglitazone, pioglitazone, troglitazone, and rosiglitazone); and related insulin sensitizers, such as selective and non-selective activators of PPAR $\alpha$ , PPAR $\beta$  and PPAR $\gamma$ ; dehydroepiandrosterone (also referred to as DHEA or its conjugated sulphate ester, DHEA-SO<sub>4</sub>); antigluccorticoids; TNF $\alpha$ inhibitors;  $\alpha$ -glucosidase inhibitors (such as
- 30 acarbose, miglitol, and voglibose), pramlintide (a synthetic analog of the human hormone amylin), other insulin secretagogues (such as repaglinide,

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gliquidone, and nateglinide), insulin, as well as the active agents discussed above for treating atherosclerosis.

Further provided by this invention are methods for treating obesity, as well as treating the complications of obesity, by administering a compound of  
5 the present invention. The antagonists can be identified, formulated, and administered similarly to the information described above. A FXR selective antagonist includes a partial agonist/antagonist or antagonist that exhibits about a two to about a ten-fold preference for FXR compared to another nuclear receptor such as, for example LXR  $\alpha$  or  $\beta$  with respect to potency  
10 ( $IC_{50}$ , the concentration of compound that achieves 50% of the maximum reduction in the transcription activity achieved by the compound of interest observed in the presence of a sub-maximal concentration of FXR agonist) and/or efficacy (the maximum percent inhibition of transcription observed with the compound in question).

15 The terms "obese" and "obesity" refers to, according to the World Health Organization, a Body Mass Index (BMI) greater than  $27.8 \text{ kg/m}^2$  for men and  $27.3 \text{ kg/m}^2$  for women (BMI equals weight (kg)/height ( $\text{m}^2$ ). Obesity is linked to a variety of medical conditions including diabetes and hyperlipidemia. Obesity is also a known risk factor for the development of  
20 type 2 diabetes (See, e.g., Barrett-Conner, E., *Epidemol. Rev.* (1989) 11: 172-181; and Knowler, et al., *Am. J Clin. Nutr.* (1991) 53:1543-1551).

Another example of combination therapy can be seen in treating obesity or obesity-related disorders, wherein the methods can be effectively used in combination with, for example, phenylpropanolamine, phentermine,  
25 diethylpropion, mazindol; fenfluramine, dexfenfluramine, phentiramine,  $\beta_3$  adrenoceptor agonist agents; sibutramine, gastrointestinal lipase inhibitors (such as orlistat), and leptins. Other agents used in treating obesity or obesity-related disorders include neuropeptide Y, enterostatin, cholecystokinin, bombesin, amylin, histamine  $H_3$  receptors, dopamine  $D_2$  receptors,  
30 melanocyte stimulating hormone, corticotrophin releasing factor, galanin and gamma amino butyric acid (GABA).

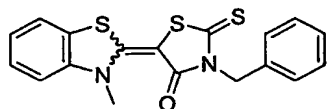


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Another example of a combination therapy can be seen in treating cholestasis, where the compounds of the invention can be combined with Actigall (Ursodeoxycholic acid - UDCA), corticosteroids, anti-infective agents (Rifampin, Rifadin, Rimactane), anti-viral agents, Vitamin D, Vitamin A, 5 phenobarbital, cholestyramine, UV light, antihistamines, oral opiate receptor antagonists and biphosphates, for the treatment, prevention, or amelioration of one or more symptoms of intrahepatic or extrahepatic cholestasis. Dosage information for these agents is well known in the art.

10 The following examples are included for illustrative purposes only and are not intended to limit the scope of the subject matter claimed herein.

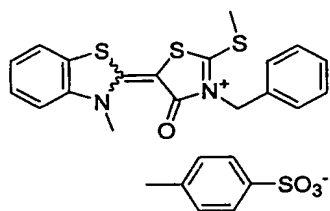
## EXAMPLE 1

**A. Preparation of 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-thioxothiazolidin-4-one**

- 5 To a 100 mL flask was added anhydrous anisole (14 mL), 2-(methylthio)benzothiazole (10.0 g, 55.2 mmol) and methyl *p*-toluenesulfonate (12.5 mL, 82.7 mmol). After heating the mixture at 120 °C for 30 min, a crystalline solid precipitated. Anisole (14 mL) was added and the mixture was further heated at 120 °C for 4 h.
- 10 After cooling to room temperature, the mixture was then transferred to a 1000 mL flask and diluted with anhydrous MeCN (200 mL). To the well-stirred mixture was added *N*-benzyl rhodanine (12.3 g, 55.1 mmol) and then dropwise TEA (12.5 mL, 90 mmol). The resulting yellow slurry was diluted with MeCN (200 mL) and stirred 2 h. The yellow precipitates were filtered
- 15 under reduced pressure, washed first with MeCN (50 mL) and then MeOH (150 mL) to give the crude product.
- To a three-neck 1 L flask fitted with a reflux condenser was added the crude product, acetone (100 mL) and MeOH (200 mL). The mixture was stirred under reflux for 15 min, cooled to room temperature, filtered under reduced
- 20 pressure, washed with MeOH (100 mL) and dried under vacuum for 24 h to yield the title product (17.4 g, 85%) as a yellow solid, which was used without further purification. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.61 (1H, dd), 7.55 (2H, m), 7.44 (1H, m), 7.25-7.34 (4H, m), 7.21 (1H, d), 5.37 (2H, s), 3.91 (3H, s); MS(ESI): 371 (MH<sup>+</sup>).

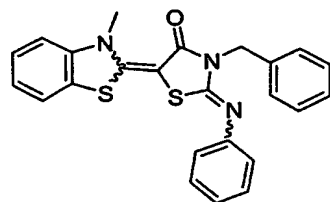
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**B. Preparation of 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate**



To a 200 mL flask was added 3-benzyl-5-(3-methylbenzothiazolin-2-ylidene)-2-thioxothiazolidin-4-one (5.00 g, 13.5 mmol), methyl *p*-toluenesulfonate (7.34 mL, 48.6 mmol) and anhydrous DMF (40 mL). After heating at 120 °C for 3 h, the mixture was allowed to cool to 60 °C, transferred to a 1 L flask and diluted with acetone (400 mL). After cooling to room temperature, the precipitate was filtered under reduced pressure, washed first with acetone (50 mL) and then Et<sub>2</sub>O (100 mL), and dried under vacuum for 12 h to give the title product (6.25 g, 83%) as a yellow crystalline solid, which was used without further purification. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.83 (1H, d), 7.75 (2H, m), 7.59-7.66 (2H, m), 7.50 (1H, m), 7.37-7.43 (5H, m), 7.06 (2H, d), 5.31 (2H, s), 4.52 (3H, s), 3.22 (3H, s), 2.28 (3H, s).

**C. Preparation of 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-phenylimino-thiazolidine-4-one**



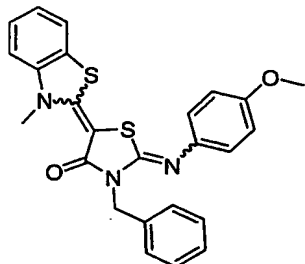
To an 8 mL vial was added 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate (100 mg, 0.18 mmol), aniline (16 μL, 0.18 mmol) and anhydrous MeCN (1 mL). After warming the mixture to 50°C, TEA (0.10 mL, 0.56 mmol) was added and continued heating the mixture at 50 °C for 12 h. After cooling to room temperature, the resulting precipitates were filtered under reduced pressure, washed with MeCN (2 mL) and dried under vacuum to yield the title product

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(22.3 mg, 29%) as a yellow solid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.59 (2H, m), 7.48 (1H, dd), 7.26-7.39 (6H, m), 7.10-7.18 (2H, m) 7.01 (3H, m), 5.16 (2H, s), 3.71 (3H, s); MS(ESI): 430 ( $\text{MH}^+$ ).

**EXAMPLE 2**

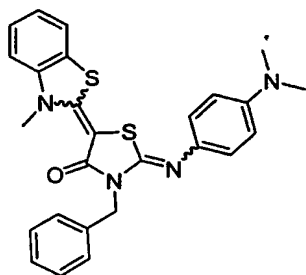
**5 Preparation of 3-benzyl-2-(4-methoxyphenylimino)-5-(3-methyl-3H-benzothiazol-2-ylidene)thiazolidine-4-one.**



The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 4-anisidine.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.58 (2H, d), 7.48 (1H, d), 7.26-7.35 (4H, m), 7.15 (1H, t), 7.01 (1H, d), 6.96 (2H, d), 6.90 (2H, d), 5.16 (2H, s), 3.82 (3H, s), 3.73 (3H, s); MS(ESI): 460 ( $\text{MH}^+$ ).

**EXAMPLE 3**

**15 Preparation of 3-benzyl-2-(4-dimethylaminophenylimino)-5-(3-methyl-3H-benzothiazol-2-ylidene)thiazolidine-4-one.**

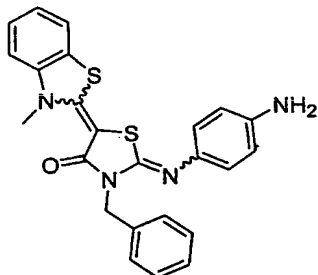


The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with *N,N*-dimethyl-1,4-phenyldiamine.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.59 (2H, d), 7.47 (1H, d), 7.24-7.35 (4H, m), 7.14 (1H, t), 6.99 (1H, d), 6.95 (2H, dd), 6.76 (2H, dd), 5.15 (2H, s), 3.73 (3H, s), 2.95 (6H, s); MS(ESI): 473 ( $\text{MH}^+$ ).

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**EXAMPLE 4**

**Preparation of 2-(4-aminophenylimino)-3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)thiazolidine-4-one.**

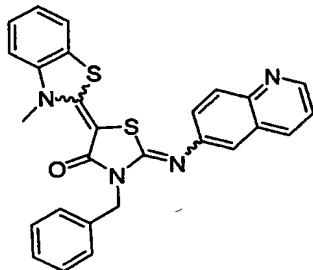


- 5 The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 1,4-phenylenediamine. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.58 (2H, m), 7.47 (1H, dd), 7.27-7.34 (4H, m), 7.14 (1H, m), 6.99 (1H, d), 6.85 (2H, dd), 6.70 (2H, dd), 5.14 (2H, s), 3.72 (3H, s), 3.60 (2H, br); MS(ESI): 445 (MH<sup>+</sup>).

10

**EXAMPLE 5**

**Preparation of 3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-2-(quinolin-6-ylimino)-thiazolidine-4-one**

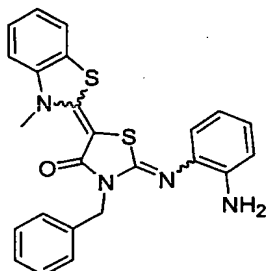


- 15 The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 6-aminoquinoline. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.84 (1H, dd), 8.09 (2H, d), 7.62 (2H, m), 7.50 (1H, d), 7.43 (1H, dd), 7.27-7.40 (6H, m), 7.16 (1H, m), 7.01 (1H, d), 5.20 (2H, s), 3.69 (3H, s); MS(ESI): 481 (MH<sup>+</sup>).

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**EXAMPLE 6**

**Preparation of 2-(2-aminophenylimino)-3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)thiazolidine-4-one**

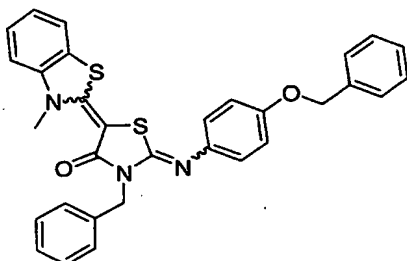


5 The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 1,2-phenylenediamine. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.48-7.56 (3H, m), 7.30-7.36 (3H, m), 7.26-29 (1H, m), 7.17 (1H, t), 7.03 (1H, d), 6.91-6.99 (2H, m), 6.69-6.77 (2H, m), 5.19 (2H, s), 3.75 (3H, s), 3.49 (2H, s); MS(ESI): 445 (MH<sup>+</sup>).

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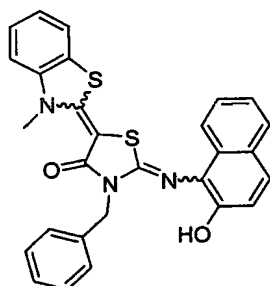
**EXAMPLE 7**

**Preparation of 3-benzyl-2-(4-benzyloxyphenylimino)-5-(3-methyl-3H-benzothiazol-2-ylidene)thiazolidine-4-one**



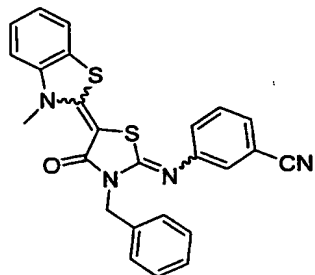
15 The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 4-benzyloxyaniline. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.58 (2H, d), 7.43-7.50 (3H, m), 7.40 (2H, t), 7.26-7.36 (5H, m), 7.15 (1H, t), 6.93-7.03 (5H, m), 5.14 (2H, s), 5.07 (2H, s), 3.73 (3H, s); MS(ESI): 536 (MH<sup>+</sup>).

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**EXAMPLE 8****Preparation of 3-benzyl-2-(2-hydroxy-1-naphthylimino)-5-(3-methyl-3H-benzothiazol-2-ylidene)thiazolidine-4-one**

- 5        The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 1-amino-2-naphthol hydrochloride. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.79 (1H, d), 7.56-7.64 (3H, m), 7.51 (2H, t), 7.28-7.44 (6H, m), 7.21 (1H, d), 7.18 (1H, t), 6.99 (1H, d), 5.34 (2H, s), 5.00 (1H, s), 3.57 (3H, s); MS(ESI): 496 (MH<sup>+</sup>).

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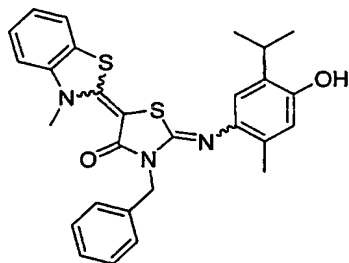
**EXAMPLE 9****Preparation of 3-[3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile**

- 15        The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 3-aminobenzonitrile. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ 7.72 (1H, d), 7.54 (2H, d), 7.23-7.41 (9H, m), 7.16-7.22 (1H, m), 5.02 (2H, s), 3.74 (3H, s); MS(ESI): 455 (MH<sup>+</sup>).

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## EXAMPLE 10

**Preparation of 3-benzyl-2-(4-hydroxy-5-isopropyl-2-methylphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one**

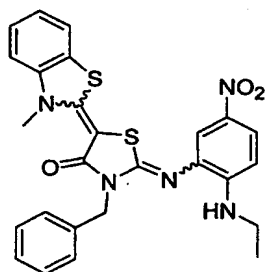


5 The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 4-aminothymol hydrochloride. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.55-7.60 (2H, m), 7.48 (1H, d), 7.26-7.34 (4H, m), 7.14 (1H, m), 6.99 (1H, d), 6.76 (1H, s), 6.62 (1H, s), 5.17 (2H, s), 4.49 (1H, s), 3.71 (3H, s), 3.17 (1H, m), 1.96 (3H, s), 1.24 (6H, d); MS(ESI): 502 (MH<sup>+</sup>).

10

## EXAMPLE 11

**Preparation of 3-benzyl-2-(2-ethylamino-5-nitrophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one**



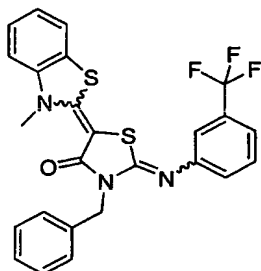
15 The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with *N*<sup>1</sup>-ethyl-4-nitrobenzene-1,2-diamine. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.98 (1H, dd), 7.93 (1H, d), 7.55 (1H, d), 7.44 (2H, d), 7.19-7.42 (6H, m), 7.11 (1H, d), 6.46 (1H, d), 5.20 (2H, s), 4.55 (1H, br), 3.83 (3H, s), 3.07 (2H, m), 1.05 (3H, t); MS(ESI): 518 (MH<sup>+</sup>).



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**EXAMPLE 12**

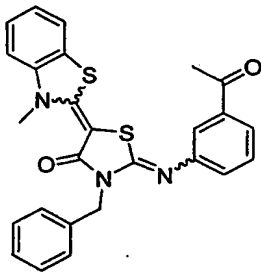
**Preparation of 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-[3-(trifluoromethyl)-phenylimino]thiazolidine-4-one**



- 5** The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 3-(trifluoromethyl)aniline. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.57 (2H, m), 7.50 (1H, d), 7.46 (1H, t), 7.24-7.42 (6H, m), 7.15-7.21 (2H, m), 7.03 (1H, d), 5.15 (2H, s), 3.73 (3H, s); MS(ESI): 498 (MH<sup>+</sup>).

**EXAMPLE 13**

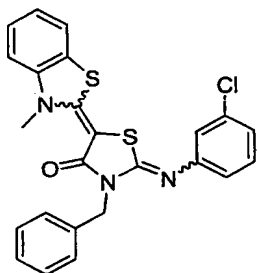
- 10 Preparation of 2-(3-acetylphenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one**



- The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 3'-aminoacetophenone. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.72 (1H, m), 7.56-7.60 (3H, m), 7.50 (1H, dd), 7.45 (1H, t), 7.27-7.37 (4H, m), 7.21 (1H, ddd), 7.17 (1H, m), 7.02 (1H, d), 5.16 (2H, s), 3.72 (3H, s), 2.61 (3H, s); MS(ESI): 472 (MH<sup>+</sup>).

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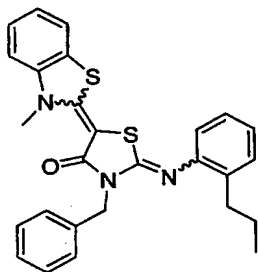
## EXAMPLE 14

**Preparation of 3-benzyl-2-(3-chlorophenylimino)-5-(3-methyl-3H-benzothiazol-2-ylidene)thiazolidine-4-one**

- 5 The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 3-chloroaniline.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.54-7.58 (2H, m), 7.49 (1H, dd), 7.26-7.36 (5H, m), 7.17 (1H, m), 7.09 (1H, ddd), 7.03 (1H, d), 7.01 (1H, t), 6.89 (1H, ddd), 5.13 (2H, s), 3.74 (3H, s); MS(ESI): 464 ( $\text{MH}^+$ ).

10

## EXAMPLE 15

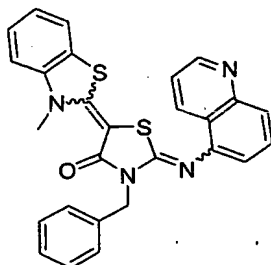
**Preparation of 3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-2-(2-propyl-phenylimino)thiazolidine-4-one**

- 15 The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 2-propylaniline.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.49 (1H, d), 7.27-7.37 (4H, m), 7.12-7.23 (3H, m), 7.06 (1H, m), 7.00 (1H, d), 6.92 (1H, d), 5.17 (2H, s), 3.71 (3H, s), 2.37 (2H, t), 1.42 (2H, s), 0.79 (3H, t); MS(ESI): 472 ( $\text{MH}^+$ ).

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## EXAMPLE 16

Preparation of 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(quinolin-5-ylimino)-thiazolidine-4-one

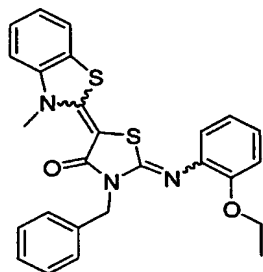


- 5 The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 5-aminoquinoline. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.86 (1H, d), 8.02 (1H, d), 7.81 (1H, d), 7.68 (1H, t), 7.42-7.50 (3H, m), 7.25-7.35 (5H, m), 7.20 (1H, d), 7.12 (1H, t), 7.07 (1H, d), 5.19 (2H, s), 3.67 (3H, s); MS(ESI): 481 (MH<sup>+</sup>).

10

## EXAMPLE 17

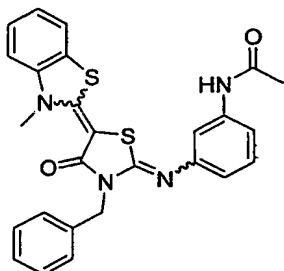
Preparation of 3-benzyl-2-(2-ethoxyphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one



- 15 The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with *o*-phenetidine. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.66 (2H, m), 7.46 (2H, d), 7.24-7.34 (3H, m), 7.07-7.16 (2H, m), 6.94-7.00 (4H, m), 5.19 (2H, s), 4.01 (2H, q), 3.69 (3H, s), 1.36 (3H, t); MS(ESI): 474 (MH<sup>+</sup>).

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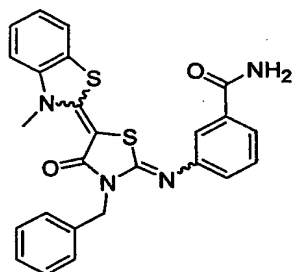
## EXAMPLE 18

**Preparation of *N*-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}acetamide**

5        The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 3'-aminoacetanilide. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.57 (2H, d), 7.48 (1H, d), 7.27-7.39 (6H, m), 7.15 (2H, m), 7.06 (1H, br s), 7.01 (1H, d), 6.76 (1H, d), 5.14 (2H, s), 3.72 (3H, s), 2.18 (3H, s); MS(ESI): 487 (MH<sup>+</sup>).

10

## EXAMPLE 19

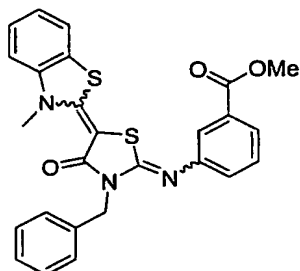
**Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzamide**

15        The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 3-aminobenzamide. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ 7.98 (1H, br s), 7.74 (1H, d), 7.62 (1H, d), 7.34-7.48 (9H, m), 7.30 (1H, m), 7.21 (1H, m), 7.12 (1H, d), 5.06 (2H, s), 3.75 (3H, s); MS(ESI): 473 (MH<sup>+</sup>).

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**EXAMPLE 20**

**Preparation of 3-[3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzoic acid, methyl ester**

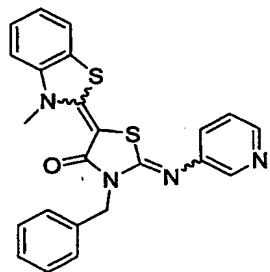


5 The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with methyl 3-aminobenzoate. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.80 (1H, m), 7.68 (1H, m), 7.56-7.60 (2H, m), 7.49 (1H, dd), 7.42 (1H, m), 7.27-7.36 (4H, m), 7.14-7.20 (2H, m), 7.01 (1H, d), 5.16 (2H, s), 3.92 (3H, s), 3.71 (3H, s); MS(ESI): 488 (MH<sup>+</sup>).

10

**EXAMPLE 21**

**Preparation of 3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-2-(pyridin-3-ylimino)-thiazolidine-4-one**

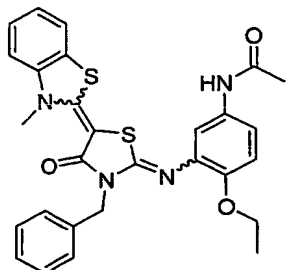


15 The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 3-aminopyridine. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.37 (1H, dd), 8.35 (1H, dd), 7.56-7.60 (2H, m), 7.51 (1H, dd), 7.27-7.37 (6H, m), 7.18 (1H, m), 7.04 (1H, d), 5.16 (2H, s), 3.73 (3H, s); MS(ESI): 431 (MH<sup>+</sup>).

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## EXAMPLE 22

Preparation of *N*-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-ethoxyphenyl]acetamido}-2-ethoxyphenylacetamide

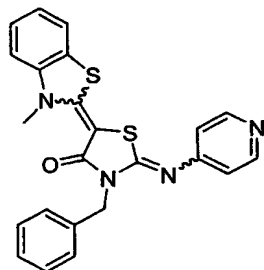


- 5 The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with *N*-(4-amino-3-ethoxyphenyl)acetamide. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.63 (2H, d), 7.48 (1H, d), 7.28-7.36 (5H, m), 7.15 (1H, t), 7.10 (1H, s), 7.00 (1H, d), 6.96 (1H, d), 6.91 (1H, d), 5.18 (2H, s), 3.97 (2H, q), 3.70 (3H, s), 2.16 (3H, s), 1.33 (3H, t); MS(ESI): 531 (MH<sup>+</sup>).

10

## EXAMPLE 23

Preparation of 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(pyridin-4-ylimino)-thiazolidine-4-one

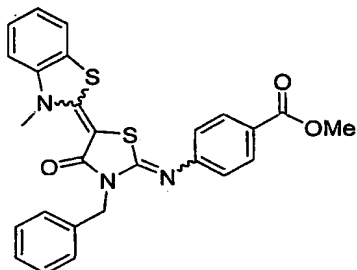


- 15 The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 4-aminopyridine. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.53 (2H, dd), 7.56 (2H, m), 7.52 (1H, dd), 7.28-7.38 (4H, m), 7.19 (1H, m), 7.06 (1H, d), 6.93 (2H, dd), 5.14 (2H, s), 3.75 (3H, s); MS(ESI): 431 (MH<sup>+</sup>).

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**EXAMPLE 24**

**Preparation of 4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzoic acid, methyl ester**

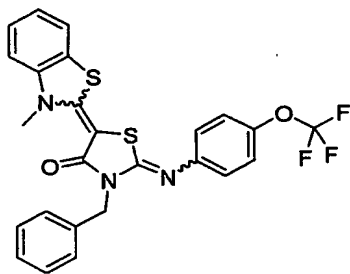


- 5 The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with methyl 4-aminobenzoate. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.04 (2H, m), 7.58 (2H, m), 7.50 (1H, d), 7.27-7.38 (4H, m), 7.17 (1H, t), 7.01-7.08 (3H, m), 5.15 (2H, s), 3.92 (3H, s), 3.72 (3H, s); MS(ESI): 488 (MH<sup>+</sup>).

10

**EXAMPLE 25**

**Preparation of 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-[4-(trifluoro-methoxy)phenylimino]thiazolidine-4-one**

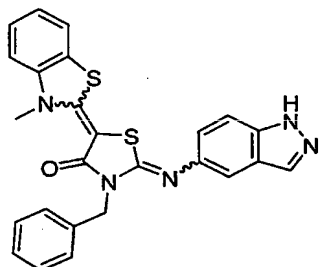


- 15 The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 4-(trifluoromethoxy)aniline. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.57 (2H, m), 7.50 (1H, dd), 7.27-7.36 (4H, m), 7.14-7.22 (3H, m), 7.03 (1H, d), 7.00 (2H, dd), 5.14 (2H, s), 3.75 (3H, s); MS(ESI): 514 (MH<sup>+</sup>).

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**EXAMPLE 26**

**Preparation of 3-benzyl-2-(1*H*-indazol-5-ylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-thiazolidin-4-one**

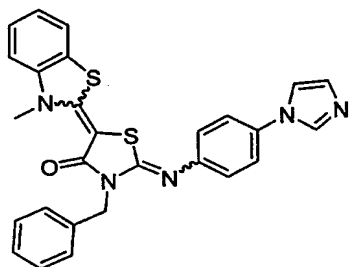


- 5 The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 5-aminoindazole. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 10.05 (1H, br s), 8.08 (1H, d), 7.64-7.67 (2H, m), 7.51-7.55 (2H, m), 7.32-7.41 (5H, m), 7.20 (1H, m), 7.14 (1H, dd), 7.04 (1H, d), 5.23 (2H, s), 3.74 (3H, s); MS(ESI): 470 (MH<sup>+</sup>).

10

**EXAMPLE 27**

**Preparation of 3-benzyl-2-(4-imidazol-1-ylphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one**



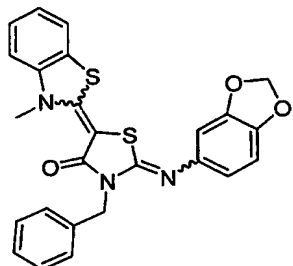
- 15 The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 4-(1*H*-imidazol-1-yl)aniline. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.93 (1H, s), 7.66 (2H, d), 7.58 (1H, d), 7.35-7.46 (7H, m), 7.29 (1H, s), 7.25 (1H, t), 7.18 (2H, m), 7.11 (1H, d), 5.24 (2H, s), 3.82 (3H, s); MS(ESI): 496 (MH<sup>+</sup>).



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**EXAMPLE 28**

**Preparation of 2-(benzo[1,3]dioxol-5-ylimino)-3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)thiazolidin-4-one**

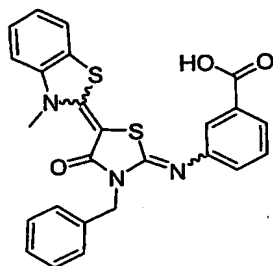


5 The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 3,4-(methylenedioxy)aniline. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.56-7.60 (2H, m), 7.49 (1H, dd), 7.28-7.36 (4H, m), 7.16 (1H, m), 7.02 (1H, d), 6.80 (1H, d), 6.56 (1H, d), 6.48 (1H, dd), 5.98 (2H, s), 5.14 (2H, s), 3.75 (3H, s); MS(ESI): 474 (MH<sup>+</sup>).

10

**EXAMPLE 29**

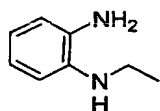
**Preparation of 3-[3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzoic acid**



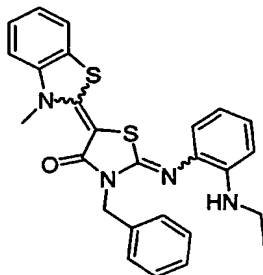
15 An aqueous solution of lithium hydroxide (1 M, 5 mL) was added to a solution of compound I-20 (0.13 g, 0.27 mmol) in THF (20 mL). After stirring at room temperature for 12 h, the reaction mixture was concentrated under reduced pressure. The resulting residue was acidified with hydrochloric acid (1 M, 10 mL) and extracted with EtOAc. The combined organic extracts were dried (anhydrous magnesium sulfate), concentrated under reduced pressure  
20 and chromatographed (silica gel, MeOH/DCM, 1:19) to yield the title compound (0.12 g, 95%) as a yellow solid. <sup>1</sup>H-NMR (MeOD-*d*<sub>3</sub>): δ 7.81 (1H,

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d), 7.63-7.68 (2H, m), 7.55 (1H, d), 7.50 (2H, d), 7.44 (1H, t), 7.31-7.40 (3H, m), 7.28 (1H, d), 7.16-7.23 (3H, m), 5.15 (2H, s), 3.79 (3H, s); MS(ESI): 474 (MH<sup>+</sup>).

**EXAMPLE 30****5 Preparation of *N*-ethyl-1,2-phenylenediamine**

*N*-Ethyl-2-nitroaniline (0.97 g, 5.8 mmol) was dissolved in EtOAc (60 mL) and placed in a closed vessel. 10% Pd/C (0.4 g, 7 mol%) was added and the mixture was hydrogenated under 50 psi H<sub>2</sub> for 2 h. The mixture was  
 10 filtered through celite and the filtrate was concentrated under reduced pressure to yield the title product (0.79 g, 99%) as a brown liquid, which was used without further purification. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 6.83 (1H, m), 6.64-6.74 (3H, m), 3.29 (3H, br s), 3.15 (2H, q), 1.30 (3H, t); TLC (2:98 MeOH/DCM R<sub>f</sub> 0.24).

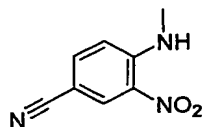
**15 Preparation of 3-benzyl-2-[2-(ethylamino)phenylimino]-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one**

The title compound was then prepared in a manner similar to that described in Example 1 by replacing aniline with *N*-ethyl-1,2-phenylenediamine. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.47-7.54 (3H, m), 7.30-7.37 (3H, m), 7.28 (1H, m), 7.17 (1H, t), 7.00-7.06 (2H, m), 6.96 (1H, dd), 6.64 (1H, m), 6.60 (1H, d), 5.19 (2H, s), 3.76 (3H, s), 3.68 (1H, br s), 3.01 (2H, q), 1.05 (3H, t); MS(ESI): 473 (MH<sup>+</sup>).

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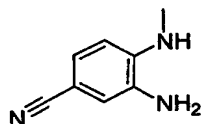
## EXAMPLE 31

## Preparation of 4-methylamino-3-nitrobenzonitrile



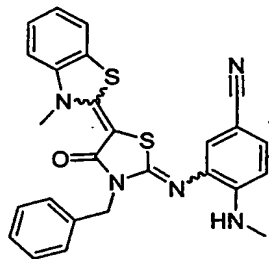
- 4-Fluoro-3-nitrobenzonitrile (0.25 g, 1.5 mmol) was cautiously added to a solution of methylamine (2.0 M, 5.0 mL) in THF. The mixture was stirred at room temperature for 8 h, concentrated under reduced pressure, and chromatographed (silica gel, DCM) to give the title product (0.18 g, 68%) as a yellow solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.52 (1H, d), 8.41 (1H, br s), 7.64 (1H, dd), 6.92 (1H, d), 3.10 (3H, d).

## 10 Preparation of 3-amino-4-(methylamino)benzonitrile



- 4-Methylamino-3-nitrobenzonitrile (0.18 g, 1.0 mmol) was dissolved in EtOAc (10 mL) and placed in a closed vessel. 10% Pd/C (50 mg, 5 mol%) was added and the mixture was hydrogenated via a hydrogen-filled balloon that was affixed to the vessel. After 2 h the mixture was filtered through celite and the filtrate was concentrated under reduced pressure to yield the title product (0.14 g, 93%) as an off-white solid, which was used without further purification. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.19 (1H, dd), 6.92 (1H, d), 6.57 (1H, d), 4.04 (1H, br s), 3.30 (2H, br s), 2.91 (3H, br s); TLC (5:95 MeOH/DCM R<sub>f</sub> 0.33).

## 20 Preparation of 3-[3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(methylamino)benzonitrile

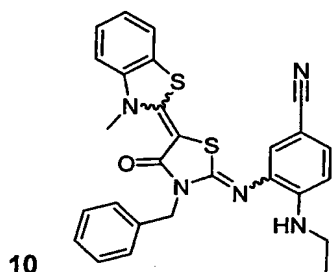


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The title compound was then prepared in a manner similar to that described in Example 1 by replacing aniline with 3-amino-4-(methylamino)benzonitrile. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.55 (1H, d), 7.42-7.47 (2H, m), 7.34-7.41 (3H, m), 7.28-7.34 (2H, m), 7.21 (1H, m), 7.18 (1H, d), 7.11 (1H, d), 6.45 (1H, d), 5.17 (2H, s), 4.15 (1H, br s), 3.83 (3H, s), 2.63 (3H, br s); MS(ESI): 484 (MH<sup>+</sup>).

**EXAMPLE 32**

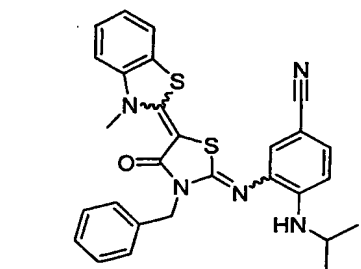
**Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(ethylamino)benzonitrile**



The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with ethylamine. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.54 (1H, d), 7.41-7.46 (2H, m), 7.27-7.40 (5H, m), 7.18-7.24 (2H, m), 7.11 (1H, d), 6.49 (1H, d), 5.18 (2H, s), 4.23 (1H, t), 3.83 (3H, s), 3.01 (2H, m), 1.02 (3H, t); MS(ESI): 498 (MH<sup>+</sup>).

**EXAMPLE 33**

**Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(isopropylamino)benzonitrile**



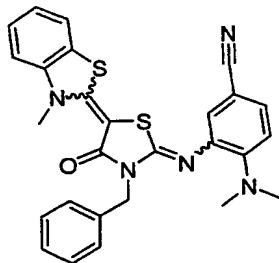
The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with isopropylamine. <sup>1</sup>H-NMR

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(CDCl<sub>3</sub>):  $\delta$  7.54 (1H, d), 7.45 (2H, d), 7.27-7.40 (5H, m), 7.18-7.24 (2H, m), 7.11 (1H, d), 6.53 (1H, d), 5.18 (2H, s), 4.29 (1H, d), 3.83 (3H, s), 3.54 (1H, m), 1.02 (6H, d); MS(ESI): 512 (MH<sup>+</sup>).

**EXAMPLE 34**

**5 Preparation of 3-[3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(dimethylamino)benzonitrile**

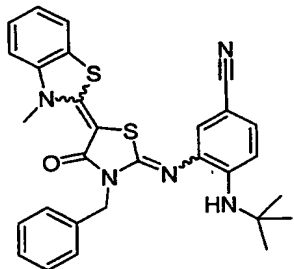


The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with dimethylamine. <sup>1</sup>H-NMR

**10** (CDCl<sub>3</sub>):  $\delta$  7.49-7.53 (3H, m), 7.27-7.37 (5H, m), 7.18 (1H, t), 7.13 (1H, d), 7.06 (1H, d), 6.85 (1H, d), 5.18 (2H, s), 3.76 (3H, s), 2.68 (6H, s); MS(ESI): 498 (MH<sup>+</sup>).

**EXAMPLE 35**

**15 Preparation of 3-[3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(tert-butylamino)benzonitrile**

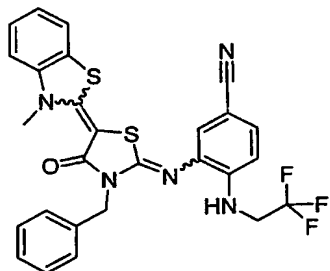


The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with *tert*-butylamine. <sup>1</sup>H-NMR

**20** (CDCl<sub>3</sub>):  $\delta$  7.54 (1H, d), 7.44 (2H, d), 7.27-7.40 (5H, m), 7.18-7.24 (2H, m), 7.11 (1H, d), 6.80 (1H, d), 5.18 (2H, s), 4.67 (1H, br s), 3.83 (3H, s), 1.22 (9H, s); MS(ESI): 526 (MH<sup>+</sup>).

## EXAMPLE 36

Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(2,2,2-trifluoroethylamino)benzonitrile.

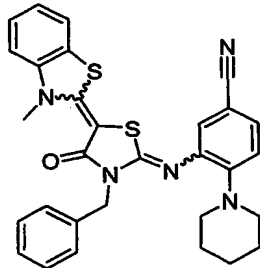


5 The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with 2,2,2-trifluoroethylamine. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.57 (1H, d), 7.27-7.44 (8H, m), 7.23 (1H, t), 7.14 (1H, d), 6.62 (1H, d), 5.17 (2H, s), 4.49 (1H, t), 3.86 (3H, s), 3.50 (2H, m); MS(ESI): 552 (MH<sup>+</sup>).

10

## EXAMPLE 37

Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-piperidin-1-ylbenzonitrile

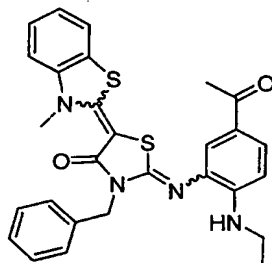


15 The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with piperidine. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.50-7.54 (3H, m), 7.27-7.37 (5H, m), 7.18 (1H, t), 7.15 (1H, d), 7.05 (1H, d), 6.92 (1H, d), 5.17 (2H, s), 3.75 (3H, s), 2.98 (4H, m), 1.44 (6H, m); MS(ESI): 538 (MH<sup>+</sup>).

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**EXAMPLE 38**

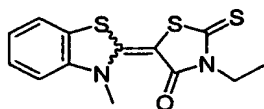
**Preparation of 2-[5-acetyl-2-(ethylamin )phenylimino]-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one**



- 5 The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with ethylamine and by replacing 4-fluoro-3-nitrobenzonitrile with 4'-chloro-3'-nitroacetophenone. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.68 (1H, dd), 7.65 (1H, d), 7.53 (1H, d), 7.45-7.49 (2H, m), 7.32-7.38 (3H, m), 7.28-7.31 (1H, m), 7.19 (1H, m), 7.06 (1H, d), 6.52 (1H, d), 5.19 (2H, s), 4.24 (1H, t), 3.78 (3H, s), 3.06 (2H, m), 2.51 (3H, s), 1.05 (3H, t); MS(ESI): 515 (MH<sup>+</sup>).
- 10

**EXAMPLE 39**

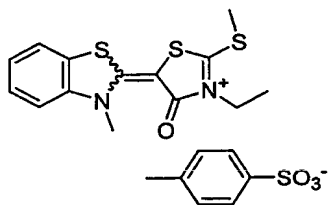
**Preparation of 3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-thioxothiazolidin-4-one**



- 15 The title compound was prepared in a manner similar to that described in Example 1 by replacing *N*-benzyl rhodanine with *N*-ethyl rhodanine. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.63 (1H, d), 7.45 (1H, m), 7.30 (1H, m), 7.22 (1H, d), 4.24 (2H, q), 3.91 (3H, s), 1.32 (3H, t); MS(ESI): 309 (MH<sup>+</sup>).

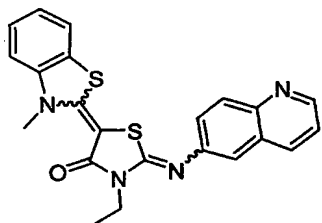
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**Preparation 3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate**



The title compound was prepared from 3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-thioxothiazolidin-4-one and methyl *p*-toluenesulfonate in a manner similar to that described in Example 1. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.82 (1H, d), 7.77 (2H, d), 7.58-7.66 (2H, m), 7.49 (1H, m), 7.08 (2H, d), 4.52 (3H, s), 4.21 (2H, q), 3.29 (3H, s), 2.29 (3H, s), 1.45 (3H, t).

**Preparation of 3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(quinolin-6-ylimino)-thiazolidin-4-one**



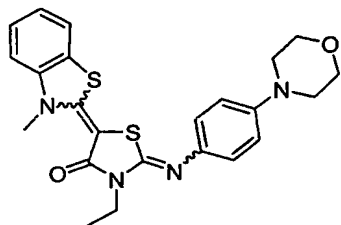
The title compound was prepared from 3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate and 6-aminoquinoline in a manner similar to that described in Example 1. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.85 (1H, dd), 8.11 (1H, d), 8.10 (1H, d), 7.51 (1H, dd), 7.46 (1H, dd), 7.40 (1H, d), 7.38 (1H, dd), 7.32 (1H, m), 7.16 (1H, m), 7.01 (1H, d), 4.10 (2H, q), 3.70 (3H, s), 1.41 (3H, t); MS(ESI): 419 (MH<sup>+</sup>).



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## EXAMPLE 40

**Preparation of 3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-morpholin-4-yl-phenylimino)thiazolidin-4-one**

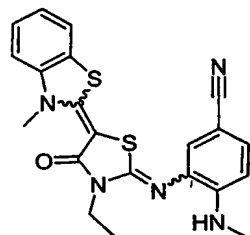


- 5        The title compound was prepared in a manner similar to that described in Example 39 by replacing 6-aminoquinoline with 4-morpholin-4-ylaniline. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.49 (1H, dd), 7.31 (1H, m), 7.15 (1H, m), 6.91-7.02 (5H, m), 4.03 (2H, q), 3.88 (4H, m), 3.73 (3H, s), 3.17 (4H, m), 1.36 (3H, t); MS(ESI): 453 (MH<sup>+</sup>).

10

## EXAMPLE 41

**Preparation of 3-[3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(methylamino)benzonitrile**

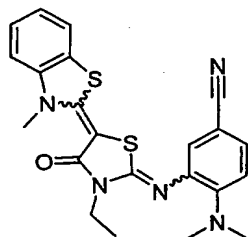


- 15        The title compound was prepared in a manner similar to that described in Example 39 by replacing 6-aminoquinoline with 3-amino-4-(methylamino)benzonitrile. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.53 (1H, d), 7.36 (1H, m), 7.36 (1H, dd), 7.25 (1H, m), 7.20 (1H, m), 7.09 (1H, d), 6.60 (1H, d), 4.86 (1H, q), 4.07 (2H, q), 3.81 (3H, s), 2.92 (3H, d), 1.37 (3H, t); MS(ESI): 422 (MH<sup>+</sup>).

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**EXAMPLE 42**

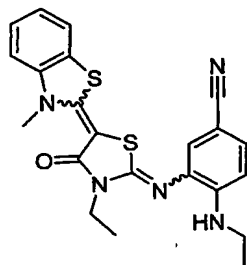
**Preparation of 4-dimethylamino-3-[3-thyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile**



- 5 The title compound was prepared in a manner similar to that described in Example 39 by replacing 6-aminoquinoline with 3-amino-4-(dimethylamino)benzonitrile. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.52 (1H, dd), 7.34 (1H, m), 7.34 (1H, dd), 7.20 (1H, d), 7.18 (1H, m), 7.06 (1H, d), 6.92 (1H, d), 4.08 (2H, q), 3.76 (3H, s), 2.90 (6H, s), 1.38 (3H, t); MS(ESI): 436 (MH<sup>+</sup>).

**EXAMPLE 43**

**Preparation of 4-ethylamino-3-[3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile**

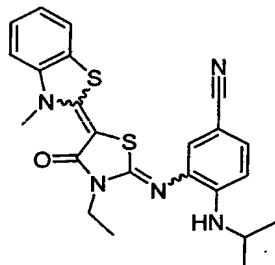


- 15 The title compound was prepared in a manner similar to that described in Example 39 by replacing 6-aminoquinoline with 3-amino-4-(ethylamino)benzonitrile. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.53 (1H, d), 7.32-7.40 (2H, m), 7.26 (1H, m), 7.20 (1H, m), 7.10 (1H, d), 6.60 (1H, d), 4.75 (1H, t), 4.08 (2H, q), 3.81 (3H, s), 3.22 (2H, m), 1.37 (3H, t), 1.29 (3H, t); MS(ESI): 436 (MH<sup>+</sup>).

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**EXAMPLE 44**

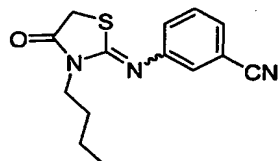
**Preparation of 3-[3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(isopropylamino)benzonitrile**



- 5        The title compound was prepared in a manner similar to that described in Example 39 by replacing 6-aminoquinoline with 3-amino-4-(isopropylamino)benzonitrile. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.53 (1H, dd), 7.36 (1H, m), 7.32 (1H, dd), 7.25 (1H, d), 7.20 (1H, m), 7.10 (1H, d), 6.60 (1H, d), 4.74 (1H, d), 4.08 (2H, q), 3.81 (3H, s), 3.67 (1H, m), 1.37 (3H, t), 1.25 (6H, d);
- 10    MS(ESI): 450 (MH<sup>+</sup>).

**EXAMPLE 45**

**Preparation of 3-(3-butyl-4-oxothiazolidin-2-ylideneamino)benzonitrile**



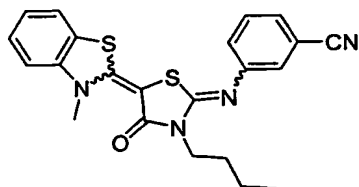
- To a 250 mL flask was added 3-aminobenzonitrile (0.59 g, 5.0 mmol),
- 15    CHCl<sub>3</sub> (25 mL) and saturated sodium bicarbonate (25 mL). To the well-stirred mixture was added dropwise thiophosgene (0.39 mL, 5.1 mmol). After 2h butylamine (0.50 mL, 5.1 mmol) was added dropwise and stirred 1 h. The reaction mixture was then extracted with CHCl<sub>3</sub>, concentrated under reduced pressure, and chromatographed (silica gel, 2:98 MeOH/DCM) to yield 1-butyl-
- 20    3-(3-cyanophenyl)thiourea (1.02 g, 87%) as a white solid: TLC (2:98 MeOH/DCM R<sub>f</sub> 0.47).

To a 100 mL flask was added anhydrous EtOH (25 mL), 1-butyl-3-(3-cyanophenyl)thiourea (0.99 g, 4.2 mmol); ethyl chloroacetate (0.51 mL, 5.0

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mmol), and anhydrous pyridine (0.5 mL, 5 mmol). After heating under reflux 16 h, the product mixture was concentrated under reduced pressure and chromatographed (silica gel, 2:98 MeOH/DCM) to afford the title product (0.78 g, 67%) as a colorless oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.40-7.47 (2H, m), 7.25 (1H, m), 7.19 (1H, m), 3.84 (2H, t), 3.84 (2H, s), 1.69 (2H, m), 1.39 (2H, m), 0.97 (3H, t); MS(ESI): 274 (MH<sup>+</sup>).

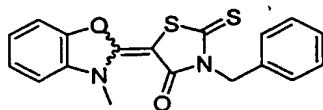
**Preparation of 3-[3-butyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile**



To a 8 mL vial was added 3-(3-butyl-4-oxothiazolidin-2-ylideneamino)benzonitrile (55 mg, 0.20 mmol), 3-methyl-2-(methylthio)benzothiazol-3-ium *p*-toluenesulfonate (73 mg, 0.20 mmol), anhydrous MeCN (2 mL) and TEA (70 μL, 0.50 mmol). The reaction mixture was first warmed to 50 °C and the resulting solution was allowed to stir at room temperature for 16 h. The product mixture was concentrated under reduced pressure, chromatographed (silica gel, 1:99 MeOH/DCM) and then recrystallized from MeCN to give the title product (11.8 mg) as a yellow solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.52 (1H, dd), 7.38-7.48 (2H, m), 7.32-7.37 (2H, m), 7.25 (1H, m), 7.18 (1H, m), 7.06 (1H, d), 3.96 (2H, t), 3.75 (3H, s), 1.77 (2H, m), 1.44 (2H, m), 0.98 (3H, t); MS(ESI): 421 (MH<sup>+</sup>).

**EXAMPLE 46**

**Preparation of 3-benzyl-5-(3-methyl-3*H*-benzoxazol-2-ylidene)-2-thioxothiazolidin-4-one**

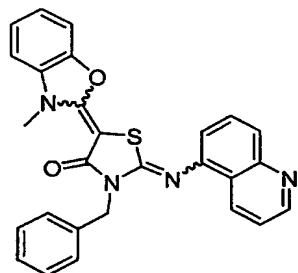


The title compound was prepared in a manner similar to that described in Example 1 by replacing 2-(methylthio)benzothiazole with 2-

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m raptobenzoxazole.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.49 (2H, d), 7.24-7.41 (6H, m), 7.18 (1H, d), 5.31 (2H, s), 4.17 (3H, s); MS(ESI): 377 ( $\text{MNa}^+$ ).

**Preparation of 3-benzyl-5-(3-methyl-3*H*-benzoxazol-2-ylidene)-2-(quinolin-5-ylimino)-thiazolidin-4-one**



5

To a 10 mL flask was added 3-benzyl-5-(3-methyl-3*H*-benzoxazol-2-ylidene)-2-thioxothiazolidin-4-one (100 mg, 0.28 mmol), anhydrous  $\text{CHCl}_3$  (2 mL) and methyl *p*-toluenesulfonate (53  $\mu\text{L}$ , 0.35 mmol). After heating at reflux 10 min, the reaction mixture was heated at 120  $^\circ\text{C}$  for 2 h to yield a red oil.

10 The desired intermediate, 3-benzyl-5-(3-methyl-3*H*-benzoxazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate, was not isolated successfully in previous experiments similar to Example 1 and, thus, the crude reaction mixture was diluted with anhydrous  $\text{CHCl}_3$  (4 mL) and used without purification in the next step.

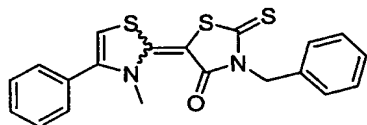
15 To a 8 mL vial was added the crude reaction mixture (2 mL) and 5-aminoquinoline (29 mg, 0.20 mmol). After warming the mixture to 55  $^\circ\text{C}$ , TEA (0.10 mL, 0.56 mmol) was added and the mixture was heated at 60  $^\circ\text{C}$  for 16 h. After cooling to room temperature, the resulting product mixture was concentrated under reduced pressure and chromatographed (silica gel, 2:98

20 MeOH/DCM) to yield the title product (21 mg) as a yellow solid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.86 (1H, dd), 7.97 (1H, dd), 7.85 (1H, d), 7.66 (1H, dd), 7.56 (2H, m), 7.30-7.42 (3H, m), 7.19-7.25 (3H, m), 7.11-7.17 (2H, m), 7.05 (1H, d), 5.24 (2H, s), 4.11 (3H, s); MS(ESI): 465 ( $\text{MH}^+$ ).

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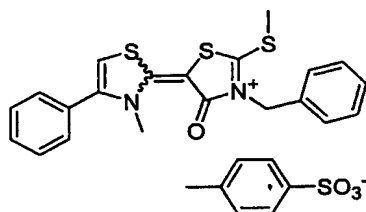
## EXAMPLE 47

**Preparation of 3'-benzyl-3-methyl-4-phenyl-2'-thioxo-2',3'-dihydro-3H-[2,5']bithiazol-yliden-4'-one**



- 5 The title compound was prepared in a manner similar to that described in Example 1 by replacing 2-(methylthio)benzothiazole with 2-mercapto-4-phenylthiazole. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.49-7.56 (5H, m), 7.34-7.38 (2H, m), 7.24-7.33 (3H, m), 6.54 (1H, s), 5.39 (2H, s), 3.68 (3H, s); MS(ESI): 397 (MH<sup>+</sup>).

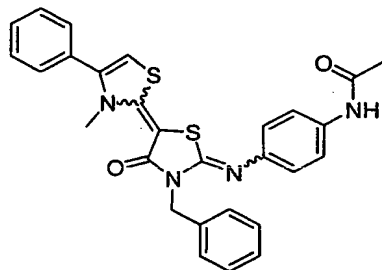
- 10 **Preparation 3'-benzyl-3-methyl-2'-methylthio-4'-oxo-4-phenyl-3H,4'H-[2,5']bithiazol-yliden-3'-ium p-toluenesulfonate**



- The title compound was prepared from 3'-benzyl-3-methyl-4-phenyl-2'-thioxo-2',3'-dihydro-3H-[2,5']bithiazol-yliden-4'-one and methyl p-toluenesulfonate in a manner similar to that described in Example 1. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.72 (2H, d), 7.49-7.56 (3H, m), 7.42-7.47 (2H, m), 7.36-7.41 (5H, m), 7.05 (2H, d), 6.99 (1H, s), 5.29 (2H, s), 4.26 (3H, s), 3.14 (3H, s), 2.29 (3H, s).
- 15

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**Preparation of *N*-[4-(3'-benzyl-3-methyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-[2,5']-bithiazolyliden-2'-yliden amin )phenyl]acetamid**

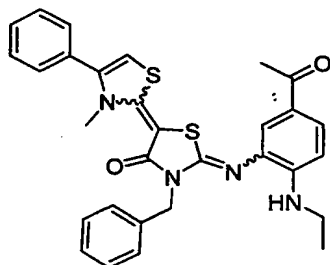


The title compound was prepared from 3'-benzyl-3-methyl-2'-methylthio-4'-oxo-4-phenyl-3*H*,4'*H*-[2,5']bithiazolyliden-3'-ium *p*-toluenesulfonate and 4'-aminoacetanilide in a manner similar to that described in Example 1. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.56 (2H, d), 7.42-7.47 (5H, m), 7.24-7.34 (5H, m), 7.12 (1H, s), 6.97 (2H, d), 6.30 (1H, s), 5.15 (2H, s), 3.49 (3H, s), 2.17 (3H, s); MS(ESI): 513 (MH<sup>+</sup>).

10

**EXAMPLE 48**

**Preparation of 2'-[5-acetyl-2-(ethylamino)phenylimino]-3'-benzyl-3-methyl-4-phenyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one**



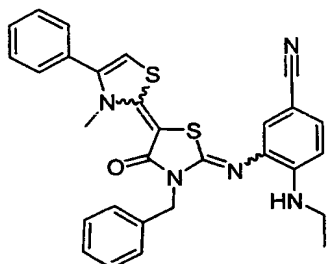
The title compound was prepared in a manner similar to that described in Example 47 by replacing 4'-aminoacetanilide with 3'-amino-4'-(ethylamino)acetophenone. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.63-7.67 (2H, m), 7.44-7.48 (5H, m), 7.27-7.37 (5H, m), 6.50 (1H, d), 6.37 (1H, s), 5.20 (2H, s), 4.29 (1H, t), 3.55 (3H, s), 3.05 (2H, m), 2.49 (3H, s), 1.04 (3H, t); MS(ESI): 541 (MH<sup>+</sup>).

15

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**EXAMPLE 49**

**Preparation of 3-(3'-benzyl-3-methyl-4'-oxo-4-phenyl-3',4'-dihydro-3H-[2,5']bithiazol-yliden-2'-ylideneamino)-4-(ethylamino)benzonitrile**

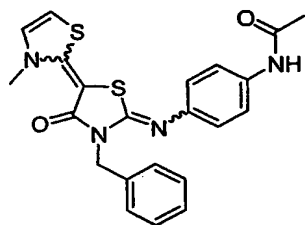


- 5 The title compound was prepared in a manner similar to that described in Example 47 by replacing 4'-aminoacetanilide with 3-amino-4-(ethylamino)benzonitrile. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.46-7.50 (3H, m), 7.41-7.45 (2H, m), 7.23-7.40 (6H, m), 7.21 (1H, d), 6.47 (1H, d), 6.40 (1H, s), 5.18 (2H, s), 4.27 (1H, t), 3.59 (3H, s), 3.00 (2H, m), 1.01 (3H, t); MS(ESI): 524 (MH<sup>+</sup>).

10

**EXAMPLE 50**

**Preparation of N-[4-(3'-benzyl-3-methyl-4'-oxo-3',4'-dihydro-3H-[2,5']bithiazol-yliden-2'-ylideneamino)phenyl]acetamide**



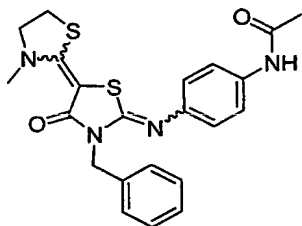
- 15 The title compound was prepared in a manner similar to that described in Example 47 by replacing 2-mercapto-4-phenylthiazole with 2-mercaptothiazole. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.55 (2H, d), 7.44 (2H, d), 7.24-7.33 (3H, m), 7.13 (1H, s), 6.95 (2H, d), 6.52 (1H, d), 6.37 (1H, d), 5.12 (2H, s), 3.68 (3H, s), 2.17 (3H, s); MS(ESI): 437 (MH<sup>+</sup>).



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## EXAMPLE 51

Preparation of *N*-[4-(3'-benzyl-3-methyl-4'-oxo-[2,5']bithiazolidinyliden-2'-ylidene-amino)phenyl]acetamide

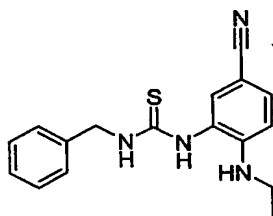


5 The title compound was prepared in a manner similar to that described in Example 47 by replacing 2-mercapto-4-phenylthiazole with 2-methylthio-2-thiazoline. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.53 (2H, d), 7.44 (2H, d), 7.23-7.32 (3H, m), 7.14 (1H, s), 6.93 (2H, d), 5.07 (2H, s), 3.63 (2H, t), 3.16 (3H, s), 3.09 (2H, t), 2.17 (3H, s); MS(ESI): 439 (MH<sup>+</sup>).

10

## EXAMPLE 52

Preparation of 1-benzyl-3-(5-cyano-2-ethylaminophenyl)thiourea

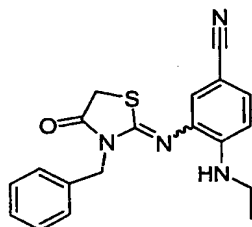


To a 100 mL flask was added 3-amino-4-(ethylamino)benzonitrile (1.0 g, 6.2 mmol), anhydrous THF (50 mL) and benzylisothiocyanate (0.92 g, 6.2 mmol). The reaction mixture was heated at 50 °C with stirring for 6 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and chromatographed (silica gel, 1:1 EtOAc/Hex) to yield the title product (1.78 g, 93 %). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.48 (1H, dd), 7.37 (1H, d), 7.31 (3H, m), 7.24 (1H, s), 7.18 (1H, br), 6.67 (1H, d), 5.95 (1H, br), 4.81 (2H, d), 4.68 (1H, br), 3.19 (2H, m), 1.23 (3H, t).

20

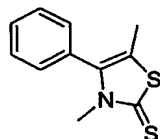
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**Preparation of 3-(3-benzyl-4-oxothiazolidin-2-ylideneamino)-4-(ethylamino)benzo-nitril**



- To a 100 mL flask was added 1-benzyl-3-(5-cyano-2-ethylaminophenyl)thiourea (1.0 g, 3.2 mmol), anhydrous ethanol (40 mL), ethyl chloroacetate (0.39 g, 3.2 mmol) and then DBU (0.58 g, 3.8 mmol). The reaction was heated at 80 °C for 30 min. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and chromatographed (silica gel, 1:1 EtOAc/Hex) to afford the title product (0.98 g, 87 %). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.38 (6H, m), 7.11 (1H, d), 6.50 (1H, d), 5.05 (2H, s), 3.96 (2H, s), 3.01 (2H, m), 1.03 (3H, t).

**Preparation of 3,5-dimethyl-4-phenyl-3H-thiazole-2-thione**

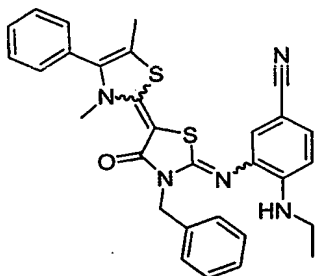


- To a 100 mL flask was added freshly prepared triethylammonium methylidithiocarbamate (2.0 g, 9.5 mmol), anhydrous MeCN (50 mL), and 2-bromopropiophenone (2.04 g, 9.5 mmol). The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the resulting crude residue was treated with conc H<sub>2</sub>SO<sub>4</sub> (5 mL) with stirring at room temperature. After 20 min, the reaction mixture was diluted with water (75 mL) and then mixed with DCM (75 mL). The layers were separated and the aqueous layer extracted once more with DCM (75 mL). The combined organic layers were washed with water (3 x 50 mL) and then brine (50 mL), dried over anhydrous MgSO<sub>4</sub> and concentrated under reduced pressure to afford the title product (1.95 g, 92%) as an off -

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white solid, which was used without further purification.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.50 (2H, m), 7.27 (2H, m), 3.45 (3H, s), 2.06 (3H, s).

**Preparation of 3-(3'-benzyl-3,5-dimethyl-4'-oxo-4-phenyl-3',4'-dihydro-3H-[2,5']-bithiazolylden-2'-ylideneamino)-4-(ethylamino)benzonitrile**



5

To an 8 mL vial was added 3,5-dimethyl-4-phenyl-3H-thiazole-2-thione (100 mg, 0.45 mmol), methyl *p*-toluenesulfonate (126 mg, 0.68 mmol) and anhydrous anisole (0.5 mL). The reaction was heated to 120 °C and stirred for 3h. The cooled reaction mixture was diluted with anhydrous MeCN (3 mL) and then treated with 3-(3-benzyl-4-oxothiazolidin-2-ylideneamino)-4-(ethylamino)benzonitrile (50 mg, 0.14 mmol) and TEA (70  $\mu\text{L}$ , 0.50 mmol). The reaction mixture was warmed to 80 °C and the resulting solution was allowed to stir for 16 h. The product mixture was concentrated under reduced pressure and chromatographed (silica gel, 1:1 EtOAc/Hex) to yield the title product (48.3 mg, 64%) as a yellow solid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.40 (5H, m), 7.33 (2H, m), 7.25 (3H, m), 7.23 (2H, m), 6.46 (1H, d), 5.18 (2H, s), 4.28 (1H, m), 3.46 (3H, s), 2.99 (2H, m), 2.28 (3H, s), 1.01 (3H, t); MS(ESI): 538 ( $\text{MH}^+$ ).

10

15

**EXAMPLE 53**

**Time Resolved Fluorescence Resonance Energy Transfer (TR-FRET)**

**20 Assay**

The FRET assay was performed by incubating 8 nM of GST-FXR-LBD, 8 nM of Europium-labeled anti-GST antibody (Wallac), 16 nM biotin-SRC-1 peptide [5'-biotin-CPSSHSSLTERHKILHRLQLQEGSPS-CONH<sub>2</sub>], 20 nM APC-SA [allophycocyanin conjugated streptavidin] (Wallac) in FRET assay buffer (20 mM  $\text{KH}_2\text{PO}_4/\text{K}_2\text{HPO}_4$  (pH 7.3), 150 mM NaCl, 2 mM CHAPS, 2 mM EDTA, 1 mM DTT) in the presence of the test compound(s) for 2-4 hours at

25

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room temperature. Data was collected using an LJL Analyst with readings at 615 nm and 665 nm.

#### EXAMPLE 54

##### FXR Co-Transfection Assay

- 5           The basic co-transfection protocol for measuring FXR activity is as follows. CV-1 African Green Monkey Kidney cells are plated 24 hours before transfection to achieve approximately 70-80 percent confluency. Cells are transfected with CMX-hFXR, CMX-RXR $\alpha$ , Luc12 reporter (ECREx7-Tk-Luciferase), and a CMX- $\beta$ -Galactosidase expression vector. The transfection reagent used is DOTAP. Cells are incubated with the DOTAP/DNA mixture for 10 5 hours after which the cells are harvested and plated onto either 96 well or 384 well plates containing the appropriate concentration of test compound. The assay is allowed to continue for an additional 18-20 hours, after which the cells are lysed, and the luciferase activity is measured on a standard plate 15 reader.

##### Results of Examples 53 and 54

- Both the FXR/ECREx7 co-transfection assay (Example 54) and the TR-FRET assay (Example 53) can be used to establish the EC<sub>50</sub>/IC<sub>50</sub> values for potency and percent activity or inhibition for efficacy. Efficacy defines the 20 activity of a compound relative to a high control (chenodeoxycholic acid, CDCA) or a low control (DMSO/vehicle). The dose response curves are generated from an 8 point curve with concentrations differing by ½ LOG units. Each point represents the average of 4 wells of data from a 384 well plate. The curve for the data is generated by using the equation:

- 25           
$$Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\text{LogEC}_{50} - X) * \text{HillSlope}))}$$

- The EC<sub>50</sub>/IC<sub>50</sub> is therefore defined as the concentration at which an agonist or antagonist elicits a response that is half way between the Top (maximum) and Bottom (baseline) values. The EC<sub>50</sub>/IC<sub>50</sub> values represented are the averages of at least 3 independent experiments. The determination of 30 the relative efficacy or % control for an agonist is by comparison to the

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maximum response achieved by chenodeoxycholic acid that is measured individually in each dose response experiment.

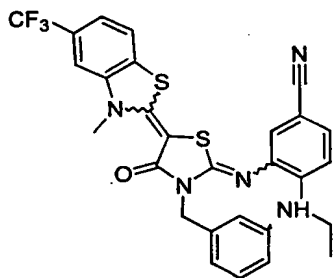
For the antagonist assay, 40  $\mu$ M CDCA is added to each well of a 384 well plate to elicit a response. The % inhibition for each antagonist is therefore a measurement of the inhibition of the activity of 40  $\mu$ M CDCA. In this example 100% inhibition would indicate that the activity of 40  $\mu$ M CDCA has been reduced to baseline levels, defined as the activity of the assay in the presence of DMSO only.

Most of the compounds disclosed herein and tested exhibited activity in at least one of the above assays ( $EC_{50}$  or  $IC_{50}$  less than 10  $\mu$ M). Most showed activity at below 1  $\mu$ M. Some showed activity below 100 nM. For example, 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(ethylamino)benzonitrile (Example 32) shows an  $EC_{50}$  of about 0.010  $\mu$ M and a % efficacy of about 150% in the co-transfection assay; and 3-(3'-benzyl-3,5-dimethyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-[2,5']-bithiazolyliden-2'-ylideneamino)-4-(ethylamino)benzonitrile (Example 52) shows an  $EC_{50}$  of about 0.056  $\mu$ M and a % efficacy of about 32% in the co-transfection assay; and an  $IC_{50}$  of about 0.042  $\mu$ M and a % inhibition of about 48% in a FRET assay.

20

**EXAMPLE 55**

**Preparation of 3-{3-benzyl-5-[3-methyl-5-(trifluoromethyl)-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-(ethylamino)benzonitrile**



25

To a suspension of 2-amino-4-(trifluoromethyl)benzenethiol hydrochloride (4.58 g, 20 mmol) in  $CHCl_3$  (50 mL) was added satd aqueous

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Na<sub>2</sub>CO<sub>3</sub> (50 mL). To this stirred biphasic mixture was added CSCI<sub>2</sub> (1.57 mL, 20 mmol) dropwise. After the addition was complete, the mixture was stirred for 72 h at 20 °C. The organic layer was separated and the aqueous layer was extracted by CHCl<sub>3</sub> (3x20 mL). The combined organic layer was washed by

5 water and dried over MgSO<sub>4</sub>. Evaporation of solvent gave 2-mercapto-5-(trifluoromethyl)benzothiazole (1.27 g), which was used in the next step without further purification. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.23 (1H, d), 6.94 (1H, s), 6.81 (1H, d), 4.53 (s, 1 H).

To a suspension of the above compound in anisole (10 mL) was added

10 methyl tosylate (MeOTs) (2.5 mL, 2 equiv) and the suspension was heated to 130 °C for 3 h. After cooling to 20 °C, acetonitrile and 3-benzylrhodanine were added. To this suspension was added TEA (3 mL, 4 equiv) dropwise, yellow precipitate appeared immediately. The suspension was stirred for 5 h at 20 °C. The yellow solid was collected by filtration and washed by acetonitrile and

15 dried under high vacuum to give the product (360 mg).

To a suspension of the above compound in DMF (4 mL) was added MeOTs (0.45 mL, 3 equiv) and the resulted suspension was heated to 130 °C for 5 h. After cooling to 20 °C, acetone was added to precipitate the product. Solid was collected by filtration and washed by acetone and dried under high

20 vacuum to afford the tosylate salt (110 mg).

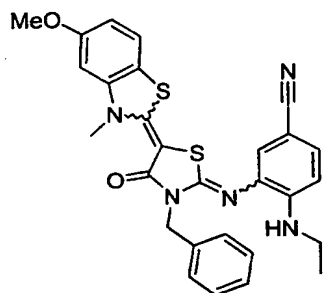
A mixture of the above compound (56 mg, 0.1 mmol), 3-amino-4-(ethylamino)benzonitrile (16 mg, 0.1 mmol) and TEA (28 µL, 0.2 mmol) was shaken at 60 °C overnight. Evaporation of solvent gave a crude, which was purified by trituration with MeOH to afford the title compound (27 mg). <sup>1</sup>H-

25 NMR indicated one isomer. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.61 (1H, d), 7.44 (2H, m), 7.35 (2H, m), 7.27-7.31 (4H, m), 7.18 (1H), 6.5 (1H), 5.19 (2H, s), 4.19 (1H, t), 3.84 (3H, s), 3.01 (2H, m), 1.03 (3H, t); MS (ESI): 566 (MH<sup>+</sup>).

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## EXAMPLE 56

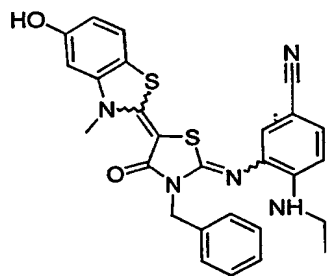
**Preparation of 3-[3-benzyl-5-(3-methyl-5-methoxy-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(ethylamino)benzonitrile**



- 5 The title compound was prepared in a manner similar to that described in Example 55 by starting from 2-mercapto-5-methoxy-benzothiazole. <sup>1</sup>H-NMR indicated one isomer. <sup>1</sup>H-NMR (DMSO-d<sub>3</sub>): δ 7.47 (1H, d), 7.13-7.21 (5H, m), 6.98 (1H, d), 6.86 (1H, d), 6.67 (1H, dd), 6.46 (1H, d), 4.96 (2H, s), 4.81 (1H, m), 3.66 (3H, s), 3.65 (3H, s), 2.89 (2H, m), 0.83 (3H, t); MS (ESI):
- 10 528 (MH<sup>+</sup>).

## EXAMPLE 57

**Preparation of 3-[3-benzyl-5-(5-hydroxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(ethylamino)benzonitrile**



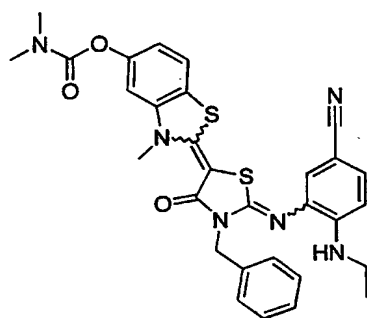
- 15 To a suspension of the product of Example 56 (1.06 g, 2 mmol) in DCM (10 mL) was added BBr<sub>3</sub> (1.0 M in DCM, 2 mL) dropwise at -78 °C. It was warmed to 20 °C slowly and the suspension was stirred for 72 h at 20 °C under N<sub>2</sub>. MeOH was added to decompose BBr<sub>3</sub> at 0 °C. Solvent was removed to give a crude, which was purified by chromatography on silica gel

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eluting with MeOH-DCM (2.5 :97.5) to afford the title compound (0.6 g). <sup>1</sup>H-NMR indicated one isomer. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 9.66 (1H, s), 7.35 (1H, d), 7.13-7.24 (5H, m), 6.99 (1H, d), 6.60 (1H, d), 6.53 (1H, dd), 6.46 (1H, d), 4.96 (2H, s), 4.82(1H, t), 3.58 (3H, s), 2.89 (2H, m), 0.84 (3H, t); MS (ESI): 514 (MH<sup>+</sup>).

**EXAMPLE 58**

**Preparation of Dimethylcarbamic acid 2-[3-benzyl-2-(5-cyano-2-ethylamino-phenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yl ester**



10

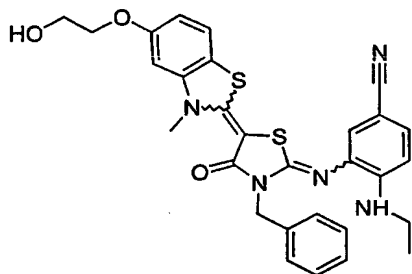
To a suspension of the product of Example 57 in CHCl<sub>3</sub> was added TEA (84 μL, 0.6 mmol) and dimethylcarbamoyl chloride (56 μL, 0.6 mmol). The resulted suspension was heated to 65 °C overnight with shaking. Solvent was removed under vacuum to give a crude, which was purified by chromatography on silica gel, eluting by MeOH-DCM (5:95) to afford the title compound (38.6 mg). <sup>1</sup>H-NMR indicated one isomer. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 9.73 (1H, d), 7.28-7.39 (7H, m), 7.14 (1H, d), 6.97 (1H, dd), 6.63 (1H, dd), 5.12 (2H, s), 4.98(1H, t), 3.78 (3H, s), 3.05 (6H, m), 2.91 (3H, s), 0.99 (3H, t); MS (ESI): 585 (MH<sup>+</sup>).



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## EXAMPLE 59

Preparation of 3-{3-benzyl-5-[5-(2-hydroxyethoxy)-3-methyl-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-(ethylamino)benzonitrile



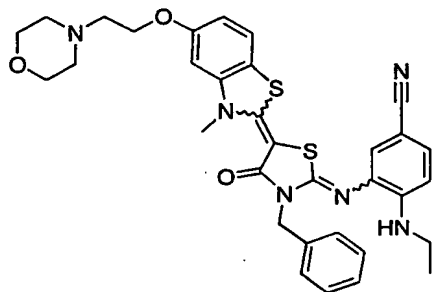
5

To a solution of the product of Example 57 in DMF were added  $K_2CO_3$  and 3-bromoethanol and the resulting suspension was heated to 75 °C with stirring under nitrogen for 72 h. Solid was removed by filtration and washed by DMF. Evaporation of solvent gave a crude, which was purified by chromatography on silica gel eluting with MeOH-DCM (5:95) to afford the title compound (0.58 g).  $^1H$ -NMR indicated one isomer.  $^1H$ -NMR (DMSO- $d_6$ ):  $\delta$  7.62 (1H, d), 7.29-7.39 (5H, m), 7.14 (1H, d), 7.02 (1H, d), 6.84 (1H, dd), 5.75 (1H, d), 5.11 (2H, s), 4.97 (1H, t), 4.87 (1H, t), 4.05 (2H, t), 3.80 (3H, s), 3.71 (2H, m), 3.05 (2H, m), 0.99 (3H, t); MS (ESI): 558 ( $MH^+$ ).

15

## EXAMPLE 60

Preparation of 3-{3-benzyl-5-[3-methyl-(2-morpholin-4-ylethoxy)-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-(ethylamino)benzonitrile



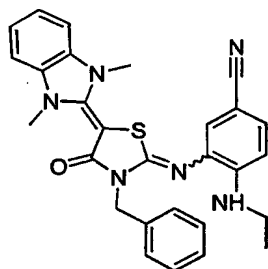
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To a suspension of the product of Example 59 (56 mg, 0.1 mmol) in anhydrous DCM (2 mL) was added triflic anhydride (Tf<sub>2</sub>O) at -10 °C under nitrogen. The suspension was stirred for 1 h at -10 °C. Morpholine (44 µL, 0.5 mmol) was added and the reaction mixture was stirred overnight at 20 °C.

- 5 Evaporation of solvent gave a crude, which was purified by chromatography on silica gel eluting with MeOH-DCM to give the title compound (18 mg). <sup>1</sup>H-NMR indicated one isomer. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.44 (2H, m), 7.39 (1H, d), 7.32-7.36 (2H, m), 7.27-7.30 (2H, m), 7.20 (1H, d), 6.78 (1H, dd), 6.67 (1H, d), 6.49 (1H, d), 5.17 (2H, s), 4.22 (1H, t), 4.15 (2H, t), 3.78 (3H, s), 3.75 (4H, m), 3.01 (2 H, m), 2.83 (2H, t), 2.59 (2 H, t), 1.02 (3 H, t); MS (ESI): 627 (MH<sup>+</sup>).
- 10

#### EXAMPLE 61

**3-[3-benzyl-5-(1,3-dimethyl-1,3-dihydrobenzoimidazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(ethylamino)benzonitrile**



15

- To suspension of 2-mercaptobenzimidazole (15.02 g, 100 mmol) in aqueous NaHCO<sub>3</sub> (25.2 g, 300 mmol in 40 mL of H<sub>2</sub>O) was added Me<sub>2</sub>SO<sub>4</sub> (47.4 mL, 500 mmol) dropwise at 20 °C. A clear solution was obtained. The solution was stirred for 17 h at 20 °C. NaI (3.2 g, 200 mmol) was added. After
- 20 the solution was cooled in an ice-water bath, yellowish precipitate appeared. Solid was collected by filtration and washed by cold water and ether. Drying under high vacuum afford the iodide salt (6.5 g).

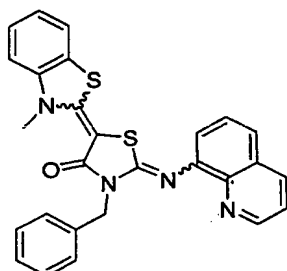
- To a solution of the above salt (66 mg, 0.2 mmol) and 3-(3-benzyl-4-oxothiazolidin-2-ylideneamino)-4-(ethylamino)benzonitrile (70 mg, 0.2 mmol)
- 25 in DMF was added DBU (62 mL, 2 equiv) and the solution was heated to 100

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°C for 48 h. Evaporation of solvent under high vacuum gave a crude, which was purified by chromatography on silica gel eluting with EtOAc-hexane (1:1) to give the title compound (3.6 mg). <sup>1</sup>H-NMR indicated one isomer. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.46 (2H, m), 7.22-7.36 (8H, m), 6.46 (1H,d), 5.17 (2H, s), 4.44  
5 (1H, t), 3.79 (3H, s), 3.01 (2 H, m), 0.88 (3 H, t); MS (ESI): 495 (MH<sup>+</sup>).

**EXAMPLE 62**

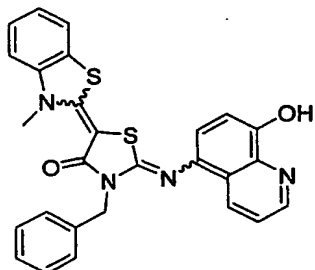
**Preparation of 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(quinolin-8-ylimino)thiazolidin-4-one**



- 5 The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 8-aminoquinoline. MS(ESI): 481 (MH<sup>+</sup>).

**EXAMPLE 63**

- 10 **Preparation of 3-benzyl-2-(8-hydroxyquinolin-5-ylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one**

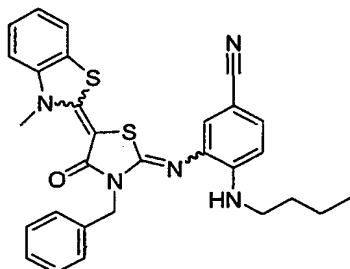


- The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 5-aminoquinolin-8-ol. MS(ESI): 497 (MH<sup>+</sup>).

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**EXAMPLE 64**

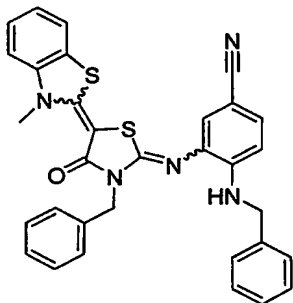
**Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-butylaminobenzonitrile**



- 5 The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with butylamine. MS(ESI): 526 (MH<sup>+</sup>).

**EXAMPLE 65**

- 10 **Preparation of 4-benzylamino-3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile**

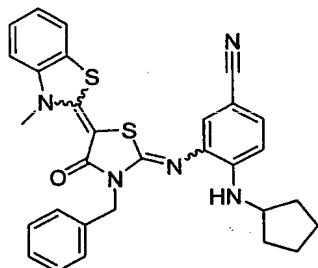


The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with benzylamine. MS(ESI): 560 (MH<sup>+</sup>).

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**EXAMPLE 66**

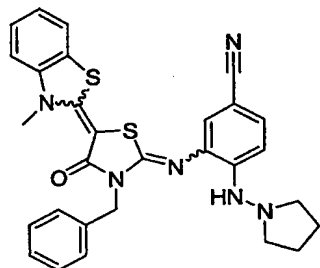
**Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-cyclopentylaminobenzonitrile**



- 5 The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with cyclopentylamine. MS(ESI): 538 (MH<sup>+</sup>).

**EXAMPLE 67**

- 10 **Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(pyrrolidin-1-ylamino)benzonitrile**

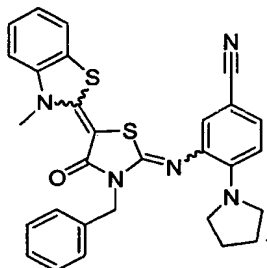


The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with 1-aminopyrrolidine. MS(ESI): 539 (MH<sup>+</sup>).

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**EXAMPLE 68**

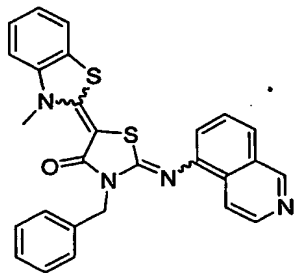
**Preparation of 3-[3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-pyrrolidin-1-ylbenzonitrile**



- 5 The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with pyrrolidine. MS(ESI): 524 (MH<sup>+</sup>).

**EXAMPLE 69**

- 10 **Preparation of 3-benzyl-2-(isoquinolin-5-ylimino)-5-(3-methyl-3H-benzothiazol-2-ylidene)thiazolidin-4-one**

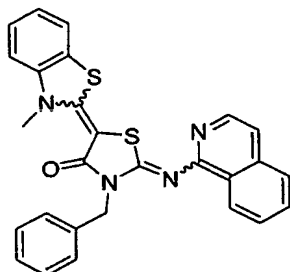


The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 5-aminoisoquinoline. MS(ESI): 481 (MH<sup>+</sup>).

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## EXAMPLE 70

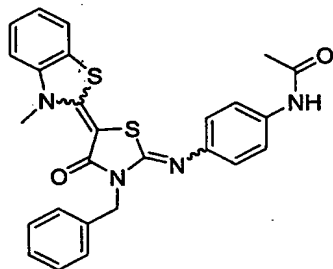
Preparation of 3-benzyl-2-(isoquinolin-1-ylimino)-5-(3-methyl-3H-benzothiazol-2-ylidene)thiazolidin-4-one



- 5 The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 1-aminoisoquinoline. MS(ESI): 481 (MH<sup>+</sup>).

## EXAMPLE 71

- 10 Preparation of N-{4-[3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylimino]phenyl}acetamide



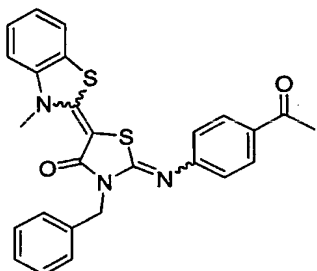
The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 4'-aminoacetanilide. MS(ESI): 487 (MH<sup>+</sup>).



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**EXAMPLE 72**

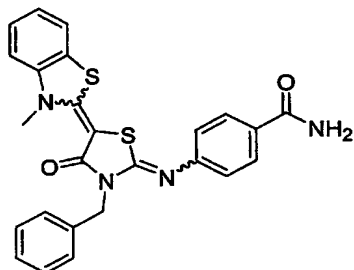
**Preparation of 2-(4-acetylphenylimino)-3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)thiazolidin-4-one**



- 5 The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 4'-aminoacetophenone. MS(ESI): 482 (MH<sup>+</sup>).

**EXAMPLE 73**

- 10 **Preparation of 4-[3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzamide**

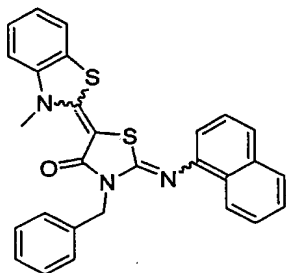


The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 4-aminobenzamide. MS(ESI): 473 (MH<sup>+</sup>).

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**EXAMPLE 74**

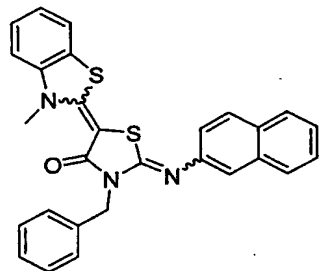
**Preparation of 3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-2-(naphthalen-1-ylimino)thiazolidin-4-one**



- 5 The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 1-naphthylamine. MS(ESI): 480 (MH<sup>+</sup>).

**EXAMPLE 75**

- 10 **Preparation of 3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-2-(naphthalen-2-ylimino)thiazolidin-4-one**

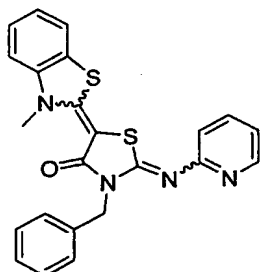


The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 2-naphthylamine. MS(ESI): 480 (MH<sup>+</sup>).

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**EXAMPLE 76**

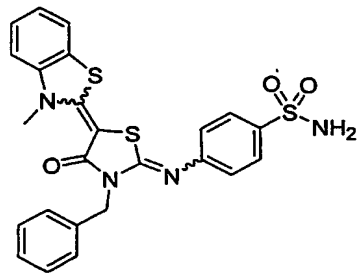
**Preparation of 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(pyridin-2-ylimino)thiazolidin-4-one**



- 5        The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 1-aminopyridine. MS(ESI): 431 (MH<sup>+</sup>).

**EXAMPLE 77**

**Preparation of 4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzenesulfonamide**

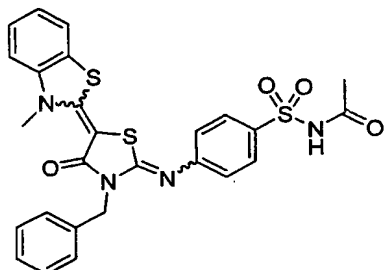


- 10       The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 4'-aminoacetophenone. MS(ESI): 509 (MH<sup>+</sup>).

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## EXAMPLE 78

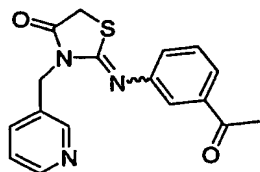
Preparation of N-acetyl-4-[3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzenesulfonamide



- 5 The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with N-acetyl-4-aminobenzenesulfonamide. MS(ESI): 551 (MH<sup>+</sup>).

## EXAMPLE 79

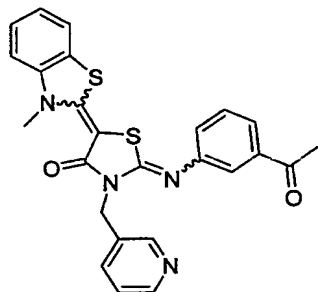
- A. Preparation of 2-(3-acetylphenylimino)-3-pyridin-3-ylmethylthiazolidin-4-one



- The title compound was prepared from 3-picolyl isothiocyanate hydrobromide and 3'-aminoacetophenone in a manner similar to Example 52.
- <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.80 (1H, d), 8.58 (1H, dd), 7.85 (1H, m), 7.74 (1H, m), 7.54 (1H, m), 7.45 (1H, m), 7.29 (1H, m), 7.15 (1H, m), 5.05 (2H, s), 3.86 (2H, s), 2.60 (3H, s).

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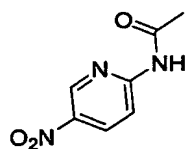
**B. Preparation of 2-(3-acetylphenylimino)-5-(3-methyl-3H-benzothiazol-2-ylidene)-3-pyridin-3-ylmethylthiazolidin-4-one**



The title compound was prepared from intermediate 2-(3-acetylphenylimino)-3-pyridin-3-ylmethylthiazolidin-4-one and 3-methyl-2-(methylthio)benzothiazol-3-ium *p*-toluenesulfonate as described in Example 45. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.87 (1H, d), 8.56 (1H, dd), 7.93 (1H, m), 7.74 (1H, m), 7.60 (1H, m), 7.53 (1H, d), 7.46 (1H, m), 7.27-7.38 (2H, m), 7.17-7.23 (2H, m), 7.05 (1H, d), 5.18 (2H, s), 3.74 (3H, s), 2.62 (3H, s); MS(ESI): 473 (MH<sup>+</sup>).

**EXAMPLE 80**

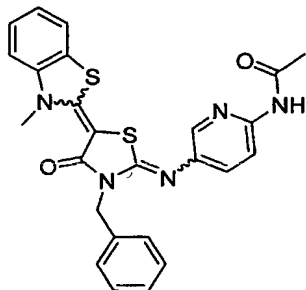
**A. Preparation of N-(5-aminopyridin-2-yl)acetamide**



To a hot solution of 2-amino-5-nitropyridine (1.4 g, 10 mmol) in acetic anhydride (5 mL) at 100°C was added conc. H<sub>2</sub>SO<sub>4</sub> (0.1 mL). The resulting mixture was heated at 130°C for 2h, cooled and partitioned between EtOAc (200 mL) and water (100 mL). The layers were separated and the aqueous layer was washed once with EtOAc (100 mL). The combined organic layers were washed with water (100 mL), saturated aqueous NaHCO<sub>3</sub> (100 mL) and then brine (50 mL); dried over anhydrous MgSO<sub>4</sub> and concentrated under reduced pressure to afford N-(5-nitropyridin-2-yl)acetamide (1.8 g, 98%), which was used without further purification. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 9.14 (1H, d), 8.50 (1H, dd), 8.40 (1H, d), 8.23 (1H, br s), 2.29 (3H, s).

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**B. Preparation of N-{5-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-yliden )-4-oxothiazolidin-2-ylideneamino]pyridin-2-yl}acetamide**

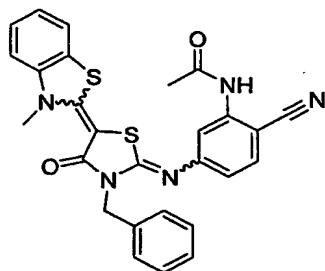


In a manner similar to Example 30, intermediate N-(5-nitropyridin-2-yl)acetamide was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ 10.45 (1H, s), 8.07 (1H, d), 7.97 (1H, d), 7.75 (1H, d), 7.33-7.46 (7H, m), 7.29 (1H, m), 7.22 (1H, m), 5.06 (2H, s), 3.79 (3H, s), 2.09 (3H, s); MS(ESI): 488 (MH<sup>+</sup>).

10

**EXAMPLE 81**

**Preparation of N-{5-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-2-cyanophenyl}acetamide**



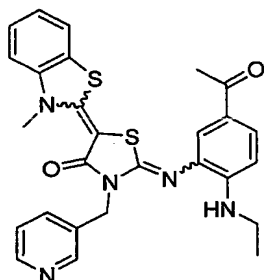
The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 5'-amino-2'-cyanoacetanilide. MS(ESI): 512 (MH<sup>+</sup>).

15

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**EXAMPLE 82**

**Preparation of 2-(5-acetyl-2-ethylaminophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-3-pyridin-3-ylmethylthiazolidin-4-one**

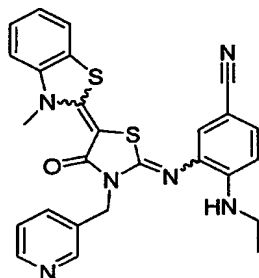


- 5        The title compound was prepared in a manner similar to that described in Example 79 by replacing 3'-aminoacetophenone with 3'-amino-4'-(ethylamino)acetophenone. MS(ESI): 516 (MH<sup>+</sup>). Recrystallization of the product from hot ethanol afforded crystals suitable for single-crystal X-ray diffraction. Structural analysis showed that the E-isomer had been obtained.

10

**EXAMPLE 83**

**Preparation of 4-ethylamino-3-[5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-3-pyridin-3-ylmethylthiazolidin-2-ylideneamino]benzonitrile**

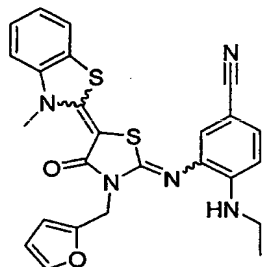


- 15        The title compound was prepared in a manner similar to that described in Example 79 by replacing 3'-aminoacetophenone with 3-amino-4-(ethylamino)benzonitrile. MS(ESI): 499 (MH<sup>+</sup>).

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**EXAMPLE 84**

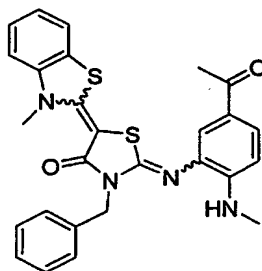
**Preparation of 4-(3-(3-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino)benzonitrile**



- 5 The title compound was prepared in a manner similar to that described in Example 83 by replacing 3-picolyl isothiocyanate hydrobromide with 2-furfuryl isothiocyanate. MS(ESI): 488 (MH<sup>+</sup>).

**EXAMPLE 85**

- 10 **Preparation of 2-(5-acetyl-2-methylaminophenylimino)-3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)thiazolidin-4-one**



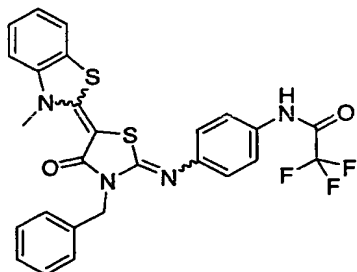
The title compound was prepared in a manner similar to that described in Example 31 by replacing 4-fluoro-3-nitrobenzonitrile with 4'-chloro-3'-nitroacetophenone. MS(ESI): 501 (MH<sup>+</sup>).



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## EXAMPLE 86

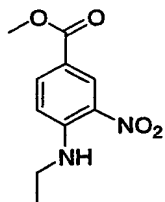
Preparation of N-{4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-2,2,2-trifluoroacetamide



- 5 The product of Example 4 was treated with trifluoroacetic anhydride in anhydrous DCM. After 1h the product mixture was diluted with EtOAc, washed with water and satd aqueous NaHCO<sub>3</sub>, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford the title compound as a yellow solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.81 (1H, br s), 7.53-7.59 (4H, m), 7.49 (1H, d), 7.27-7.36 (4H, m), 7.17 (1H, m), 7.01-7.06 (3H, m), 5.15 (2H, s), 3.73 (3H, s); MS(ESI): 541 (MH<sup>+</sup>).
- 10

## EXAMPLE 87

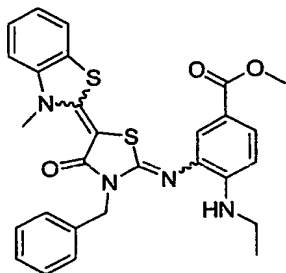
A. Preparation of 4-ethylamino-3-nitrobenzoic acid methyl ester



- 15 In a manner similar to Example 31, 4-fluoro-3-nitrobenzoic acid was treated with ethylamine to give 4-ethylamino-3-nitrobenzoic acid, which was then esterified with anhydrous hydrogen chloride in methanol to give the title compound. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.89 (1H, d), 8.28 (1H, br s), 8.06 (1H, dd), 6.87 (1H, d), 3.90 (3H, s), 3.42 (2H, m), 1.40 (3H, t).

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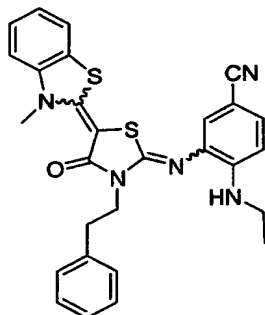
**B. Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzoic acid methyl ester**



In a manner similar to Example 30, intermediate 4-ethylamino-3-nitrobenzoic acid methyl ester was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.73 (1H, dd), 7.65 (1H, d), 7.52 (1H, dd), 7.45-7.49 (2H, m), 7.27-7.38 (4H, m), 7.18 (1H, m), 7.06 (1H, d), 6.52 (1H, d), 5.19 (2H, s), 4.14 (1H, br t), 3.85 (3H, s), 3.78 (3H, s), 3.04 (2H, m), 1.04 (3H, t); MS(ESI): 531 (MH<sup>+</sup>).

**EXAMPLE 88**

**Preparation of 4-ethylamino-3-[5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-3-phenethylthiazolidin-2-ylideneamino]benzonitrile**

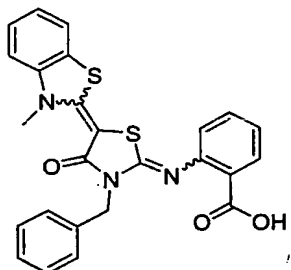


The title compound was prepared in a manner similar to that described in Example 83 by replacing 3-picoly isothiocyanate hydrobromide with phenethyl isothiocyanate. MS(ESI): 512 (MH<sup>+</sup>).

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**EXAMPLE 89**

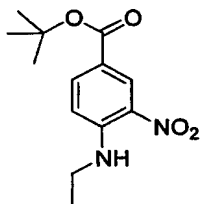
**Preparation of 2-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzoic acid**



- 5 The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with anthranilic acid. MS(ESI): 474 (MH<sup>+</sup>).

**EXAMPLE 90**

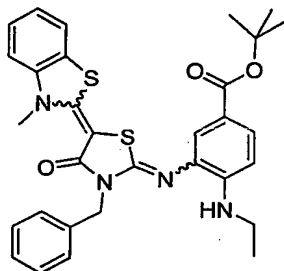
**A. Preparation of 4-ethylamino-3-nitrobenzoic acid *tert*-butyl ester**



- 10 4-Chloro-3-nitrobenzoic acid *tert*-butyl ester (3.0 g, 11.6 mmol), prepared according to a published procedure [WO 9707101], was cautiously added to a solution of 2.0 M EtNH<sub>2</sub>/THF (20 mL, 40 mmol) and TEA (2.0 mL, 14 mmol) in anhydrous THF (30 mL). The resulting mixture was heated at 65°C for 3h, cooled, concentrated under reduced pressure, diluted with DCM
- 15 (200 mL), washed with water (2 x 100 mL) and brine (50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated to give the title compound (3.1 g, 99%) as a yellow solid, which was used without further purification. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.80 (1H, d), 8.24 (1H, br s), 8.02 (1H, dd), 6.84 (1H, d), 3.41 (2H, m), 1.59 (9H, s), 1.40 (3H, t).

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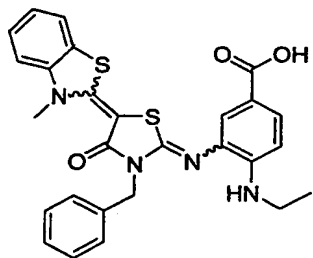
**B. Preparation of 3-[3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzoic acid *tert*-butyl ester**



- 5 In a manner similar to Example 30, intermediate 4-ethylamino-3-nitrobenzoic acid *tert*-butyl ester was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.69 (1H, dd), 7.61 (1H, d), 7.52 (1H, dd), 7.45-7.49 (2H, m), 7.27-7.37 (4H, m), 7.18 (1H, m), 7.06 (1H, d), 6.51 (1H, d), 5.19 (2H, s), 4.11 (1H, br t), 3.79 (3H, s), 3.04 (2H, m), 1.57 (9H, s), 1.04 (3H, t); MS(ESI): 573 (MH<sup>+</sup>).
- 10

**EXAMPLE 91**

**Preparation of 3-[3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzoic acid**



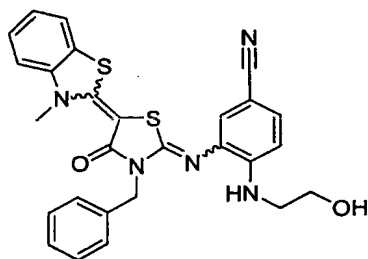
15

The product of Example 90 was treated with 55% TFA/DCM for 1h, concentrated under reduced pressure, diluted with DCM, concentrated once again, diluted with DCM, allowed to stand over solid NaHCO<sub>3</sub>, filtered and concentrated to afford the title product. MS(ESI): 517 (MH<sup>+</sup>).

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## EXAMPLE 92

**Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(2-hydroxyethylamino)benzonitrile**

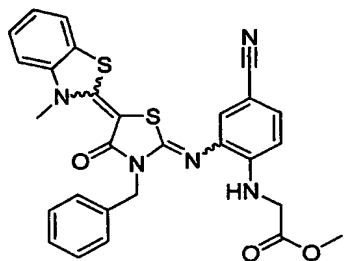


5        The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with 2-aminoethanol. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.52 (1H, d), 7.42-7.49 (4H, m), 7.27-7.37 (4H, m), 7.19 (1H, m), 7.05 (1H, d), 6.57 (1H, d), 5.94 (1H, br t), 5.19 (2H, s), 3.76 (3H, s), 3.48 (2H, m), 3.03 (2H, q), 1.23 (3H, t), 1.04 (3H, t); MS(ESI): 514 (MH<sup>+</sup>).

10

## EXAMPLE 93

**Preparation of {2-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-cyanophenylamino}acetic acid methyl ester**

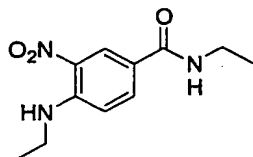


15        The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with glycine methyl ester. MS(ESI): 542 (MH<sup>+</sup>).

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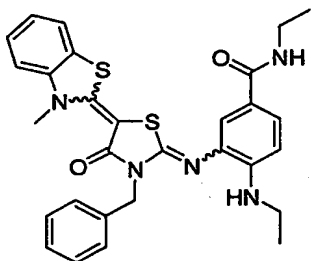
## EXAMPLE 94

## A. Preparation of N-ethyl-4-ethylamino-3-nitrobenzamide



In a manner similar to Example 31, the title compound was prepared from 4-fluoro-3-nitrobenzoic acid (as a mixed anhydride) and ethylamine. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.52 (1H, d), 8.21 (1H, br s), 7.98 (1H, dd), 6.90 (1H, d), 6.06 (1H, br s), 3.46-3.57 (2H, m), 3.38-3.45 (2H, m), 1.40 (3H, t), 1.27 (3H, t).

## B. Preparation of 3-[3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-N-ethyl-4-ethylaminobenzamide



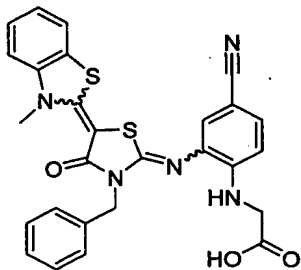
10

In a manner similar to Example 30, intermediate N-ethyl-4-ethylamino-3-nitrobenzamide was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. MS(ESI): 544 (MH<sup>+</sup>).

15

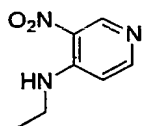
## EXAMPLE 95

## Preparation of {2-[3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-cyanophenylamino}acetic acid

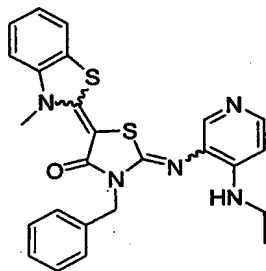


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The product of Example 93 was saponified under conditions similar to that described in Example 29 to afford the title compound. MS(ESI): 528 (MH<sup>+</sup>).

**EXAMPLE 96****5 A. Preparation of 4-ethylamino-3-nitropyridine**

In a manner similar to example 31, the title compound was prepared from 4-chloro-3-nitropyridine, prepared according to published procedure [*J. Med. Chem.* **1996**, *39*, 487-493], and ethylamine. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 9.22 (1H, s), 8.30 (1H, d), 8.10 (1H, br s), 6.71 (1H, d), 3.40 (2H, m), 1.39 (3H, t).

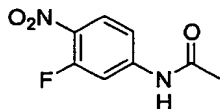
**10 B. Preparation of 3-benzyl-2-(4-ethylaminopyridin-3-ylimino)-5-(3-methyl-3H-benzothiazol-2-ylidene)thiazolidin-4-one**

In a manner similar to Example 30, intermediate 4-ethylamino-3-nitropyridine was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.04-8.09 (2H, m), 7.53 (1H, d), 7.44-7.48 (2H, m), 7.27-7.38 (4H, m), 7.19 (1H, m), 7.07 (1H, d), 6.42 (1H, d), 5.19 (2H, s), 4.12 (1H, br t), 3.79 (3H, s), 3.02 (2H, m), 1.05 (3H, t); MS(ESI): 474 (MH<sup>+</sup>).

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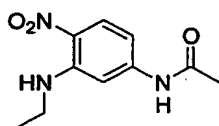
## EXAMPLE 97

## A. Preparation of 3'-fluoro-4'-nitroacetanilide



- Added 3'-fluoroacetanilide (3.06 g, 20 mmol) cautiously to conc sulfuric acid (6 mL) at 5°C. To the resulting solution, added fuming nitric acid (1.05 mL, 25 mmol) dropwise while maintaining temperature at 5-10°C. After 30 min, added ice (50 g), later diluted with water (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with saturated NaHCO<sub>3</sub> and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to give the crude product (4.0 g) as a mixture of isomers (1:1.4 ratio of 4'-nitro/2'-nitro). The desired isomer, 3'-fluoro-4'-nitroacetanilide, was isolated by flash chromatography (DCM – 5% MeOH/DCM) in low yield (1.2 g, 30%) as a yellow solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.08 (1H, app t), 7.82 (1H, dd), 7.41 (1H, br s), 7.21 (1H, m), 2.25 (3H, s).

## B. Preparation of 3'-ethylamino-4'-nitroacetanilide

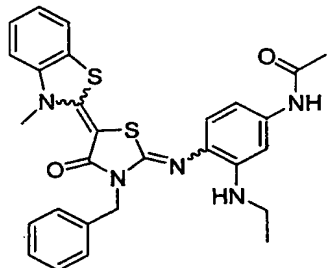


- In a manner similar to Example 31, the title compound was prepared from 3'-fluoro-4'-nitroacetanilide and ethylamine. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.17 (1H, br s), 8.13 (1H, d), 7.57 (1H, br d), 7.33 (1H, br s), 6.38 (1H, dd), 3.36 (2H, m), 2.22 (3H, s), 1.37 (3H, t).



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**C. Preparation of N-{4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-yliden amino]-3-ethylaminophenyl}acetamide**

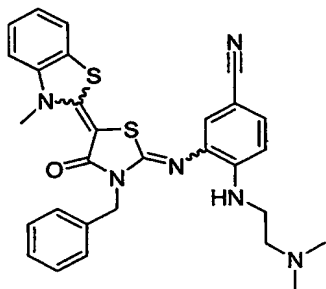


- 5 In a manner similar to Example 30, intermediate 3'-ethylamino-4'-nitroacetanilide was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.45-7.53 (3H, m), 7.27-7.37 (4H, m), 7.17 (1H, m), 7.03-7.09 (2H, m), 6.91 (1H, d), 6.83 (1H, br d), 6.75 (1H, br s), 5.18 (2H, s), 3.78 (3H, s), 2.99 (2H, m), 2.15 (3H, s), 1.03 (3H, t); MS(ESI): 530 (MH<sup>+</sup>).
- 10

**EXAMPLE 98**

**Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(2-**

- 15 **dimethylaminoethylamino)benzonitrile**

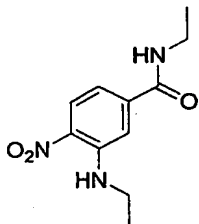


The title compound was prepared in a manner similar to that described in Example 31 by replacing methylamine with N,N-dimethylethylenediamine. MS(ESI): 541 (MH<sup>+</sup>).

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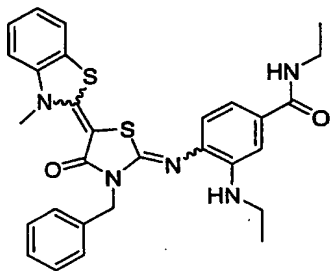
## EXAMPLE 99

## A. Preparation of N-ethyl-3-ethylamino-4-nitr benzamide



- To a chilled solution (10°C) of 3-fluoro-4-nitrobenzoyl chloride (1.0 g, 4.9 mmol) in anhydrous THF (30 mL) added dropwise 2.0 M solution of ethylamine in THF (10 mL, 20 mmol). After stirring 16h at 25°C, combine with satd NaHCO<sub>3</sub> (50 mL) and extracted with EtOAc (3 x 80 mL). The combined organic layers were washed with 1 N NaOH (50 mL) and brine (50 mL), dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to yield the title compound (0.66 g, 57%) as an orange-yellow solid that was used without further purification. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.20 (1H, d), 7.98 (1H, br s), 7.36 (1H, d), 6.81 (1H, dd), 6.13 (1H, br s), 3.51 (2H, m), 3.42 (2H, m), 1.39 (3H, t), 1.27 (3H, t).

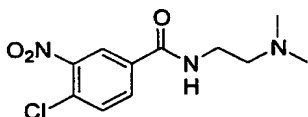
B. Preparation of 4-[3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-N-ethyl-3-ethylaminobenzamide



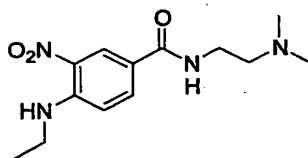
- In a manner similar to Example 30, intermediate N-ethyl-3-ethylamino-4-nitrobenzamide was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.46-7.54 (3H, m), 7.27-7.38 (4H, m), 7.19 (1H, m), 6.96-7.08 (4H, m), 6.04 (1H, br t),

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5.19 (2H, s), 3.76 (3H, s), 3.49 (2H, m), 3.06 (2H, q), 1.25 (3H, t), 1.05 (3H, t); MS(ESI): 544 (MH<sup>+</sup>).

**EXAMPLE 100****A. Preparation of 4-chloro-N-(2-dimethylaminoethyl)-3-****5 nitrobenzamide**

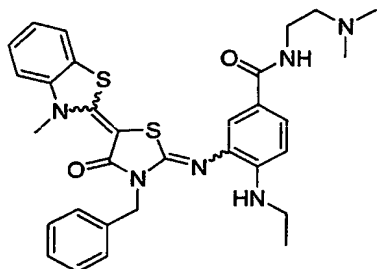
To a chilled solution (-10°C) of 4-chloro-3-nitrobenzoyl chloride (0.92 g, 4.2 mmol) in anhydrous THF (20 mL) added dropwise a solution of N,N-dimethylethylenediamine (0.44 mL, 4.0 mmol) in THF (20 mL). After stirring  
10 30 min combined with a 1:1 mixture of ice and satd NaHCO<sub>3</sub> (50 mL) and then extracted with EtOAc (3 x 80 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated and chromatographed (silica gel, MeOH/DCM, 3:22) to yield the title compound (0.40 g, 37%) as a pale yellow solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.28 (1H, d), 7.96 (1H, dd), 7.63 (1H, d), 6.98 (1H, br s), 3.54 (2H, m), 2.56 (2H, t), 2.30 (6H, s).  
15

**B. Preparation of N-(2-dimethylaminoethyl)-4-ethylamino-3-nitrobenzamide**

To 2.0 M solution of ethylamine in THF (8 mL, 16 mmol) slowly added  
20 4-chloro-N-(2-dimethylaminoethyl)-3-nitrobenzamide (0.40 g, 1.5 mmol). After heating at 65°C for 16h, the reaction mixture was cooled, concentrated and chromatographed (silica gel, MeOH/DCM, 3:22) to afford the title compound (0.30 g, 73%) as a yellow solid. <sup>1</sup>H-NMR (CD<sub>3</sub>OD): δ 8.75 (1H, d), 8.32 (1H, br s), 7.98 (1H, dd), 7.08 (1H, d), 3.58-3.64 (3H, m), 3.43-3.51 (2H, m), 2.94  
25 (2H, br t), 2.62 (6H, s), 1.35 (3H, t).

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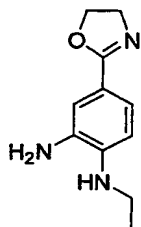
**C. Preparation of 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-N-(2-dimethylaminoethyl)-4-ethylaminobenzamide**



- 5 In a manner similar to Example 30, intermediate N-(2-dimethylaminoethyl)-4-ethylamino-3-nitrobenzamide was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound.
- <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.44-7.54 (5H, m), 7.28-7.38 (4H, m), 7.18 (1H, m), 7.04 (1H, d), 6.89 (1H, br s), 6.52 (1H, d), 5.19 (2H, s), 3.99 (1H, br t), 3.76 (3H, s), 3.59 (2H, m), 3.02 (2H, m), 2.68 (2H, br s), 2.40 (6H, s), 1.03 (3H, t); MS(ESI): 587 (MH<sup>+</sup>).
- 10

**EXAMPLE 101**

- A. Preparation of 4-(4,5-dihydrooxazol-2-yl)-N<sup>1</sup>-ethylbenzene-1,2-diamine**
- 15



- To a chilled solution (-10°C) of 4-chloro-3-nitrobenzoyl chloride (1.85 g, 8.4 mmol) in anhydrous THF (60 mL) was added dropwise a solution of ethanolamine (0.48 mL, 8.0 mmol) in THF (20 mL) followed by TEA (1.1 mL, 8.0 mmol). After stirring 1h while temperature was maintained at -10°C, the solution was combined with a 1:1 mixture of ice and satd NaHCO<sub>3</sub> (100 mL) and then extracted with EtOAc (3 x 100 mL). The combined organic layers
- 20

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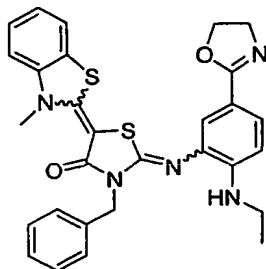
were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated to give 4-chloro-*N*-(2-hydroxyethyl)-3-nitrobenzamide (1.74 g, 89%) as a white solid, which was used without purification. TLC (3:22 MeOH/DCM  $R_f$  0.36).

- To a solution of intermediate 4-chloro-*N*-(2-hydroxyethyl)-3-nitrobenzamide (0.40 g, 1.6 mmol) in anhydrous DCM (20 mL) added dropwise thionyl chloride (0.29 mL, 4.0 mmol). After stirring 2h the reaction mixture was diluted with chloroform and concentrated. The resulting yellow oil was diluted cautiously with 2.0 M solution of ethylamine in THF (10 mL, 20 mmol) and heated in a sealed tube at 65°C. After 2h the reaction mixture was cooled, concentrated and diluted with THF (20 mL). This solution was combined with an aqueous solution of 20% KOH (5 mL) and tetrabutylammonium bromide (20 mg). After stirring rapidly 2h the mixture was extracted with  $\text{Et}_2\text{O}$  (2 x 100 mL). The combined organic layers were washed with water and brine, dried ( $\text{MgSO}_4$ ), concentrated and chromatographed (silica gel, MeOH/DCM, 1:19) to yield [4-(4,5-dihydrooxazol-2-yl)-2-nitrophenyl]ethylamine (0.17 g, 45%) as a yellow solid. TLC (1:19 MeOH/DCM  $R_f$  0.56).

- To a solution of this oxazoline intermediate (71 mg, 0.30 mmol) in ethanol (2 mL) was added zinc dust (0.20 g) and HOAc (0.20 mL). Observed initial exotherm and continued stirring 30min. The reaction mixture was diluted with  $\text{Et}_2\text{O}$  (20 mL), filtered, combined cautiously with 15%  $\text{NH}_4\text{OH}$  (10 mL), and extracted again with  $\text{Et}_2\text{O}$ . The organic layers were combined, washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated under reduced pressure to yield the title compound (60 mg, 97%) as an off-white solid, which was used without purification.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.45 (1H, dd), 7.35 (1H, d), 6.60 (1H, d), 4.38 (2H, t), 4.01 (2H, t), 3.69 (1H, br s), 3.26 (2H, br s), 3.21 (2H, m), 1.32 (3H, t); TLC (1:19 MeOH/DCM  $R_f$  0.12).

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**B. Preparation of 3-benzyl-2-[5-(4,5-dihydrooxazol-2-yl)-2-ethylamino-phenylimino]-5-(3-methyl-3*H*-benz thiazol-2-ylidene)thiazolidin-4-one**

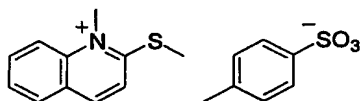


The title compound was prepared in a manner similar to Example 1 by replacing aniline with intermediate 4-(4,5-dihydrooxazol-2-yl)-N<sup>1</sup>-ethylbenzene-1,2-diamine. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.64 (1H, d), 7.55 (1H, d), 7.52 (1H, d), 7.45-7.49 (2H, m), 7.27-7.37 (4H, m), 7.18 (1H, m), 7.04 (1H, d), 6.55 (1H, d), 5.19 (2H, s), 4.38 (2H, t), 4.02 (2H, t), 3.77 (3H, s), 3.04 (2H, m), 1.05 (3H, s); MS(ESI): 542 (MH<sup>+</sup>).

10

**EXAMPLE 102**

**A. Preparation of 1-methyl-2-methylthioquinolinium *p*-toluenesulfonate**

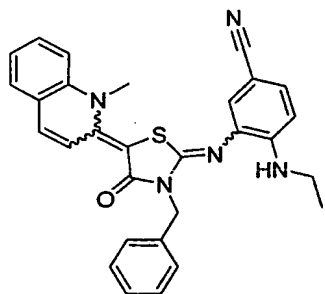


A mixture of 1-methylquinolin-2-thione (175 mg, 1.0 mmol) and methyl *p*-toluenesulfonate (186 mg, 1.0 mmol) were heated at 130°C. After 30 min the resulting solid was cooled, crushed, triturated with Et<sub>2</sub>O (4 x 1 mL) and dried under high vacuum to give the title compound (0.35 g, 97%) as a white solid. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ 8.96 (1H, d), 8.46 (1H, d), 8.35 (1H, dd), 8.16 (1H, m), 8.08 (1H, d), 7.91 (1H, m), 7.47 (2H, d), 7.10 (2H, d), 4.40 (3H, s), 3.02 (3H, s), 2.28 (3H, s).

20

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**B. Preparation of 3-[3-benzyl-5-(1-methyl-1*H*-quinolin-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile**



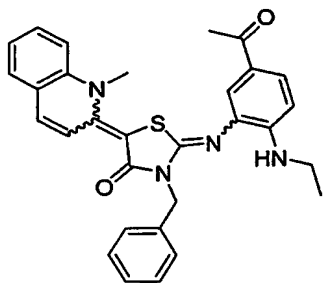
In a manner similar to Example 45, intermediate 1-methyl-2-

- 5 methylthioquinolinium *p*-toluenesulfonate was condensed with 3-(3-benzyl-4-oxothiazolidin-2-ylideneamino)-4-ethylaminobenzonitrile to afford the title compound. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.41-7.58 (4H, m), 7.20-7.38 (9H, m), 6.49 (1H, d), 5.16 (2H, s), 3.79 (3, br s), 3.01 (2H, q), 1.02 (3H, t); MS(ESI): 492 (MH<sup>+</sup>).

10

**EXAMPLE 103**

**Preparation of 2-(5-acetyl-2-ethylaminophenylimino)-3-benzyl-5-(1-methyl-1*H*-quinolin-2-ylidene)thiazolidin-4-one**



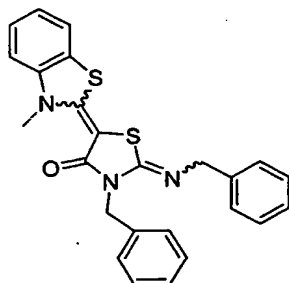
In a manner similar to Example 102, 1-methyl-2-methylthioquinolinium

- 15 *p*-toluenesulfonate was condensed with 2-(5-acetyl-2-ethylaminophenylimino)-3-benzylthiazolidin-4-one to afford the title compound. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.66-7.71 (2H, m), 7.43-7.56 (4H, m), 7.20-7.38 (7H, m), 6.53 (1H, d), 5.20 (2H, s), 3.78 (3H, br s), 3.07 (2H, q), 2.51 (3H, s), 1.06 (3H, t); MS(ESI): 509 (MH<sup>+</sup>).

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**EXAMPLE 104**

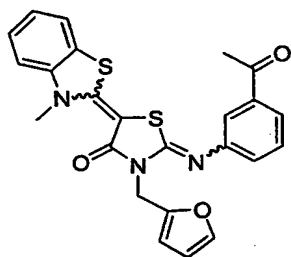
**Preparation of 3-benzyl-2-benzylimino-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one**



- 5        The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with benzylamine. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.46-7.57 (3H, m), 7.22-7.37 (9H, m), 7.15 (1H, m), 7.03 (1H, br d), 5.09 (2H, br s), 4.49 (2H, br s), 3.85 (3H, s); MS(ESI): 444 (MH<sup>+</sup>).

**EXAMPLE 105**

- 10    **Preparation of 2-(3-acetylphenylimino)-3-furan-2-ylmethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one**



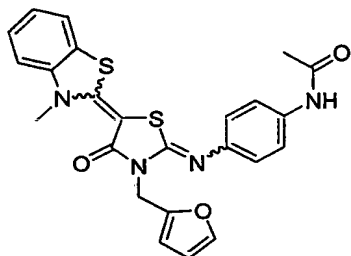
- 15        The title compound was prepared in a manner similar to that described in Example 79 by replacing 3-picolyl isothiocyanate hydrobromide with 2-furfuryl isothiocyanate. MS(ESI): 462 (MH<sup>+</sup>).



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**EXAMPLE 106**

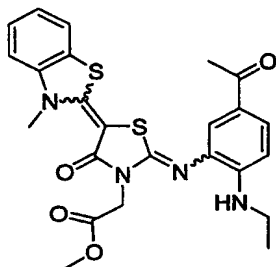
**Preparation of N-{4-[3-furan-2-ylmethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}acetamide**



- 5 The title compound was prepared in a manner similar to that described in Example 105 by replacing 3'-aminoacetophenone with 4'-aminoacetanilide. MS(ESI): 477 (MH<sup>+</sup>).

**EXAMPLE 107**

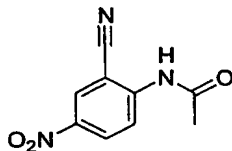
- 10 **Preparation of [2-(5-acetyl-2-ethylaminophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-3-yl]acetic acid methyl ester**



- 15 The title compound was prepared in a manner similar to Example 1 by replacing 3-benzylrhodanine with rhodanine-3-acetic acid methyl ester. MS(ESI): 497 (MH<sup>+</sup>).

**EXAMPLE 108**

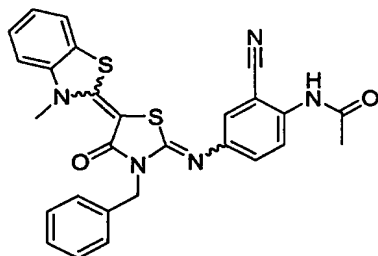
- A. **Preparation of 2-cyano-4-nitroacetanilide**



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The title compound was prepared in a manner similar to Example 80 by replacing 2-amino-5-nitropyridine with 5-nitroanthranilonitrile. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.78 (1H, d), 8.49 (1H, d), 8.44 (1H, dd), 7.88 (1H, br s), 2.35 (3H, s).

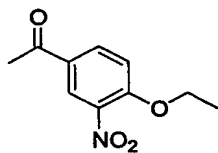
**5 B. Preparation of N-[4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-2-cyanophenyl]acetamide**



In a manner similar to Example 30, intermediate 2-cyano-4-nitroacetanilide was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.30 (1H, d), 7.49-7.57 (4H, m), 7.27-7.38 (5H, m), 7.22 (1H, d), 7.19 (1H, m), 7.07 (1H, d), 5.14 (2H, s), 3.76 (3H, s), 2.27 (3H, s); MS(ESI): 512 (MH<sup>+</sup>).

**EXAMPLE 109**

**15 A. Preparation of 4'-ethoxy-3'-nitroacetophenone**

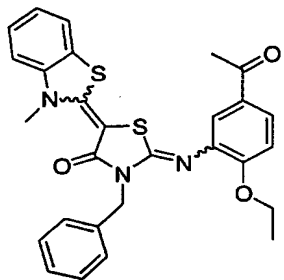


To a solution of 4'-hydroxy-3'-nitroacetophenone (1.0 g, 5.5 mmol) in anhydrous DMF (20 mL) was added anhydrous K<sub>2</sub>CO<sub>3</sub> (3.0 g, 22 mmol) and then bromoethane (0.49 mL, 6.6 mmol). After heating at 80°C for 20h, the reaction mixture was cooled, combined with satd aqueous NH<sub>4</sub>Cl (50 mL) and extracted with Et<sub>2</sub>O (2 x 100 mL). The combined organic layers were washed with water (3 x 50 mL), 1 N NaOH (50 mL) and then brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure to afford the title compound (1.1 g, 96%) as a light brown solid, which was used without further

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purification.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.41 (1H, d), 8.15 (1H, dd), 7.14 (1H, d), 4.28 (2H, q), 2.61 (3H, s), 1.52 (3H, t).

**B. Preparation of 2-(5-acetyl-2-ethoxyphenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one**



5

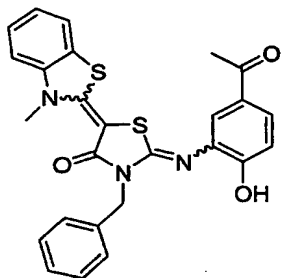
In a manner similar to Example 30, intermediate 4'-ethoxy-3'-nitroacetophenone was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.77 (1H, dd), 7.64-7.68 (2H, m), 7.61 (1H, d), 7.48 (1H, m), 7.25-7.36 (4H, m), 7.15 (1H, m), 6.99 (1H, d), 6.98 (1H, d), 5.20 (2H, s), 4.11 (2H, q), 3.69 (3H, s), 2.57 (3H, s), 1.43 (3H, t); MS(ESI): 516 ( $\text{MH}^+$ ).

10

**EXAMPLE 110**

**Preparation of 2-(5-acetyl-2-hydroxyphenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one**

15



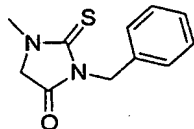
In a manner similar to Example 30, 4'-hydroxy-3'-nitroacetophenone was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. MS(ESI): 488 ( $\text{MH}^+$ ).

20

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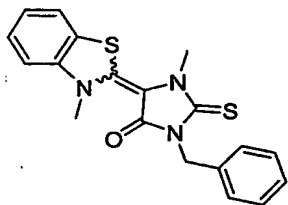
## EXAMPLE 111

## A. Preparation of 3-benzyl-1-methyl-2-thioxoimidazolidin-4-one



To a solution of sarcosine methyl ester hydrochloride (0.56 g, 4.0 mmol) and DBU (0.60 mL, 4.0 mmol) in anhydrous ethanol added benzyl isothiocyanate (0.53 mL, 4.0 mmol). The resulting solution was heated at reflux 16h, cooled, concentrated and chromatographed (silica gel, DCM) to give the title compound (0.88 g, quant.). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.49-7.53 (2H, m), 7.28-7.35 (3H, m), 5.02 (2H, s), 4.03 (2H, s), 3.34 (3H, s).

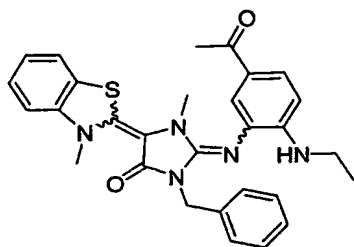
## 10 B. Preparation of 3-benzyl-1-methyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-2-thioxoimidazolidin-4-one



To a mixture of intermediate 3-benzyl-1-methyl-2-thioxoimidazolidin-4-one (0.33 g, 1.5 mmol) and 3-methyl-2-methylthiobenzothiazol-3-ium *p*-toluenesulfonate 0.66 g, 1.8 mmol) in anhydrous MeCN (10 mL) added dropwise TEA (0.28 mL, 2.0 mmol). After 2h the resulting product mixture was concentrated and chromatographed (silica gel, DCM) to afford the title compound (0.47 g, 85%) as an orange-yellow solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.54-7.61 (3H, m), 7.46 (1H, m), 7.21-7.33 (5H, m), 5.19 (2H, s), 3.86 (3H, s), 3.77 (3H, s).

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**C. Preparation of 2-(5-acetyl-2-ethylaminophenylimino)-3-benzyl-1-methyl-5-(3-methyl-3*H*-benzothiazol-2-yliden )imidazolidin-4-one**

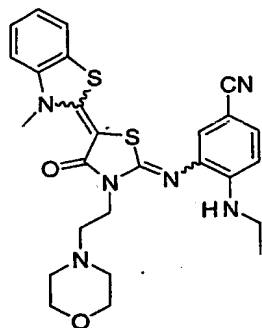


In a manner similar to Example 1, intermediate 3-benzyl-1-methyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-thioxoimidazolidin-4-one was alkylated with methyl *p*-toluenesulfonate and condensed with 3'-amino-4'-ethylaminoacetophenone to yield the title compound. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.11 (1H, d), 7.84 (1H, dd), 7.51 (1H, dd), 7.31 (1H, m), 7.16 (1H, m), 6.95-7.12 (7H, m), 6.08 (1H, br t), 4.46 (2H, hs m), 3.99 (2H, m), 3.78 (3H, s), 3.50 (3H, s), 2.65 (3H, s), 1.06 (3H, t); MS(ESI): 512 (MH<sup>+</sup>).

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## EXAMPLE 112

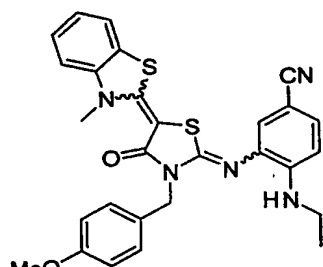
**Preparation of 4-ethylamino-3-[5-(3-methyl-3H-benzothiazol-2-ylidene)-3-(2-morpholin-4-ylethyl)-4-oxothiazolidin-2-ylideneamino]benzonitrile**



- 5 The title compound was prepared in a manner similar to that described in Example 83 by replacing 3-picolyl isothiocyanate hydrobromide with N-(2-ethylisothiocyanate)morpholine, synthesized from N-(2-aminoethyl)morpholine and thiophosgene. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.52 (1H, d), 7.32-7.37 (2H, m), 7.18-7.23 (2H, m), 7.09 (1H, d), 6.60 (1H, d), 4.75 (1H, br s), 4.16 (1H, t), 3.81 (3H, s), 3.71 (4H, br s), 3.23 (2H, q), 2.76 (2H, br s), 2.60 (4H, br s), 1.29 (3H, t); MS(ESI): 521 (MH<sup>+</sup>).
- 10

## EXAMPLE 113

**Preparation of 4-ethylamino-3-[3-(4-methoxybenzyl)-5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile**

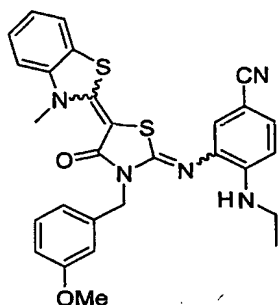


- 15 MeO The title compound was prepared in a manner similar to that described in Example 83 by replacing 3-picolyl isothiocyanate hydrobromide with 4-methoxybenzylisothiocyanate. MS(ESI): 528 (MH<sup>+</sup>).

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**EXAMPLE 114**

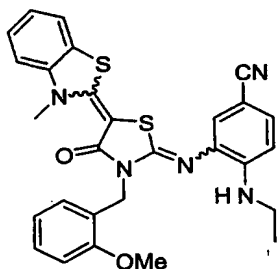
Preparation of 4-ethylamino-3-[3-(3-methoxybenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile



- 5 The title compound was prepared in a manner similar to that described in Example 83 by replacing 3-picoly isothiocyanate hydrobromide with 3-methoxybenzylisothiocyanate. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.55 (1H, d), 7.37 (1H, t), 7.22-7.32 (4H, m), 7.12 (1H, d), 7.01 (2H, m), 6.86 (1H, d), 6.51 (1H, d), 5.16 (2H, s), 4.32 (1H, t), 3.84 (3H, s), 3.81 (3H, s), 3.03 (2H, q), 1.05 (3H, t);
- 10 MS(ESI): 528 (MH<sup>+</sup>). Recrystallization of the product from hot MeCN afforded crystals suitable for single-crystal X-ray diffraction. Structural analysis showed that the E-isomer had been obtained.

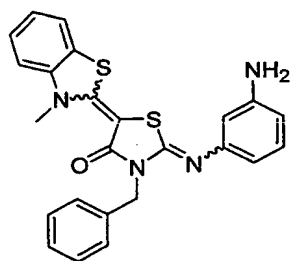
**EXAMPLE 115**

- Preparation of 4-ethylamino-3-[3-(2-methoxybenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile
- 15

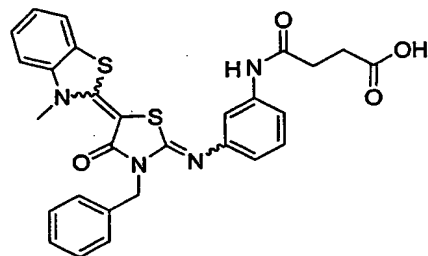


The title compound was prepared in a manner similar to that described in Example 83 by replacing 3-picoly isothiocyanate hydrobromide with 2-methoxybenzylisothiocyanate. MS(ESI): 528 (MH<sup>+</sup>).

## EXAMPLE 116

**A. Preparation of 2-(3-aminophenylimino)-3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)thiazolidine-4-one**

5        The title compound was prepared in a manner similar to that described in Example 1 by replacing aniline with 1,3-phenylenediamine. MS(ESI): 445 (MH<sup>+</sup>).

**B. Preparation of N-{3-[3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}succinamic acid**

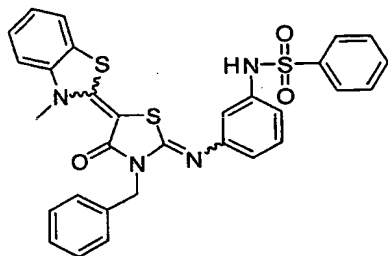
10        To a 25 mL flask was added 2-(3-aminophenylimino)-3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)thiazolidine-4-one (100 mg, 225 μmol), anhydrous DCM (5 mL) and CHCl<sub>3</sub> (3 mL). To the solution was added succinic anhydride (23 mg, 239 μmol). The reaction solution was allowed to  
15        stir at 50°C for 1.5h. The white precipitates were collected by filtration under reduced pressure, washed with DCM (10 mL) and hexanes (20 mL), and then dried under vacuum to give the title compound (75 mg, 61%). MS(ESI): 545 (MH<sup>+</sup>).



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## EXAMPLE 117

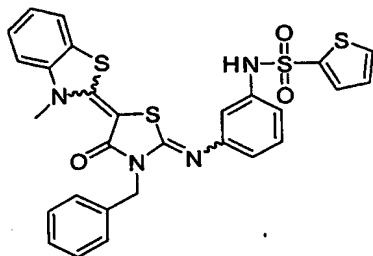
Preparation of N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}benzenesulfonamide



- 5 To a 25 mL flask was added 2-(3-aminophenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one (0.18 g, 0.40 mmol), anhydrous  $\text{CHCl}_3$  (7 mL), benzenesulfonyl chloride (56  $\mu\text{L}$ , 0.44 mmol), and TEA (0.10 mL, 0.80 mmol). The solution was stirred at 50°C for 20h. The yellow precipitates were collected by filtration under reduced pressure,
- 10 washed with hexanes (30 mL), and dried under vacuum to give the title compound (49 mg, 21%) as a yellow solid.  $^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ ):  $\delta$  7.97 (1H, s), 7.76 (2H, d), 7.53 (2H, m), 7.45 (2H, t), 7.37 (2H, d), 7.09-7.31 (8H, m), 6.81 (1H, d), 6.74 (1H, s), 6.57 (1H, d), 4.99 (2H, s), 3.72 (3H, s); MS(ESI): 585 ( $\text{MH}^+$ ).

## EXAMPLE 118

Preparation of thiophene-2-sulfonic acid {3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}amide

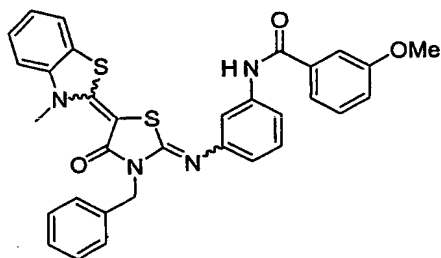


- The title compound was prepared in a manner similar to that described
- 20 in Example 117 by replacing benzenesulfonyl chloride with 2-(thiophene)sulfonyl chloride. MS(ESI): 591 ( $\text{MH}^+$ ).

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**EXAMPLE 119**

**Preparation of N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-3-methoxybenzamide**

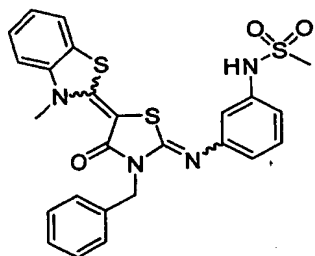


- 5 The title compound was prepared in a manner similar to that described in Example 117 by replacing benzenesulfonyl chloride with 3-methoxybenzoyl chloride. MS(ESI): 579(MH<sup>+</sup>).

**EXAMPLE 120**

**Preparation of N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}methanesulfonamide**

10

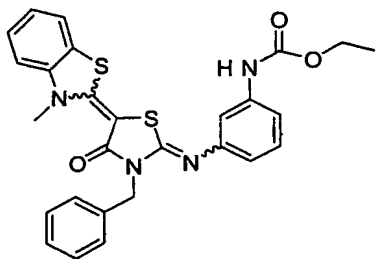


- The title compound was prepared in a manner similar to that described in Example 117 by replacing benzenesulfonyl chloride with methanesulfonyl chloride. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.88 (1H, s), 7.48 (2H, d), 7.41 (1H, d), 7.16-7.26 (5H, m), 7.09 (1H, t), 6.96 (2H, t), 6.89 (1H, m), 6.70 (1H, d), 5.05 (2H, s), 3.67 (3H, s), 2.92 (3H, s); MS(ESI): 532 (MH<sup>+</sup>).
- 15

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**EXAMPLE 121**

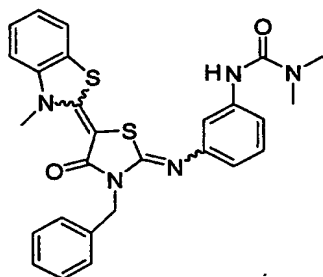
**Preparation of {3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}carbamic acid ethyl ester**



- 5 The title compound was prepared in a manner similar to the described in Example 117 by replacing benzenesulfonyl chloride with ethyl chloroformate. MS(ESI): 517 (MH<sup>+</sup>).

**EXAMPLE 122**

- 10 **Preparation of 3-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-1,1-dimethylurea**

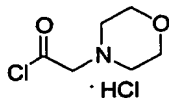


The title compound was prepared in a manner similar to the described in Example 117 by replacing benzenesulfonyl chloride with dimethylcarbamyl chloride. MS(ESI): 523(MH<sup>+</sup>).

15

**EXAMPLE 123**

**A. Preparation of morpholin-4-ylacetyl chloride hydrochloride**

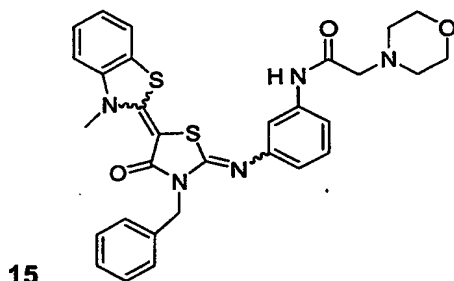


To a 100 mL flask was added morpholine (5.5 g, 63 mmol), benzene (20 mL), and ethyl chloroacetate (3.2 mL, 30 mmol). The reaction solution

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- was allowed to stir 1 h at ambient temperature. The resulting white crystalline solids were collected by filtration under reduced pressure and then transferred to a 100 mL flask along with dioxane (20 mL) and 1N NaOH (33 mL). The solution was allowed to stir at 80°C for 16h, cooled and then neutralized with
- 5 1N HCl. The aqueous solution was frozen and lyophilized to isolate the crude morpholinylacetic acid. The crude acid (2.6 g, 20 mmol) and thionyl chloride (15 mL) was added to a N<sub>2</sub>-purged 100 mL flask. After stirring 3h the reaction solution was filtered and concentrated under reduced pressure to provide the
- 10 title compound (3.1 g, 78%) as a white powder. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ 7.58 (1H, s), 3.48 (2H, s), 3.37 (4H, m), 2.76 (4H, m); <sup>13</sup>C-NMR (DMSO-*d*<sub>6</sub>): δ 166.0, 63.5, 55.5, 51.8.

**B. Preparation of N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-2-morpholin-4-ylacetamide**

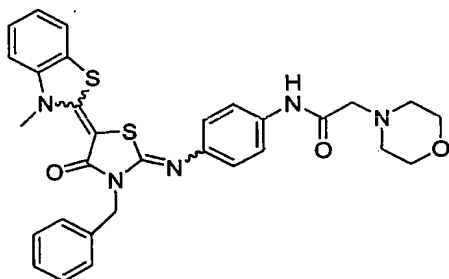


- The title compound was prepared in a manner similar to that described in Example 117 by replacing benzenesulfonyl chloride with morpholin-4-ylacetyl chloride hydrochloride. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.98 (1H, s), 7.51 (2H, d), 7.41 (1H, d), 7.34 (1H, d), 7.19-7.27 (5H, m), 7.08 (2H, m), 6.91 (1H, d), 6.70
- 20 (1H, d), 5.06 (2H, s), 3.70 (4H, t), 3.63 (3H, s), 3.07 (2H, s), 2.55 (4H, t); MS(ESI): 572 (MH<sup>+</sup>).

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**EXAMPLE 124**

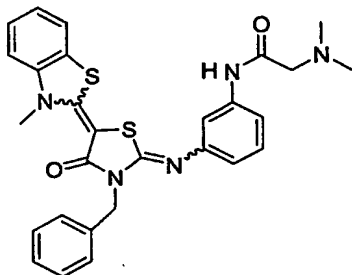
**Preparation of N-{4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-2-morpholin-4-ylacetamide**



- 5 The title compound was prepared from the product of Example 4 in a manner similar to that described in Example 123. MS(ESI): 572 (MH<sup>+</sup>).

**EXAMPLE 125**

**Preparation of N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-2-dimethylaminoacetamide**



10

- To a 25 mL flask was added N, N-dimethylglycine (500 mg, 4.85 mmol) and thionyl chloride (5 mL). The resulting solution was allowed to stir at ambient temperature under N<sub>2</sub> for 3h. The excess thionyl chloride was removed in vacuo to provide N, N-dimethylaminoacetyl chloride hydrochloride as a white powder.
- 15

- To a solution of 2-(3-aminophenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one (160 mg, 360 μmol) in chloroform (8 mL) was added N, N-dimethylaminoacetyl chloride hydrochloride (90 mg, 0.58 mmol) and TEA (150 μL, 1.1 mmol). The reaction solution was heated at reflux for 20h, cooled, and concentrated in vacuo. The crude material was
- 20

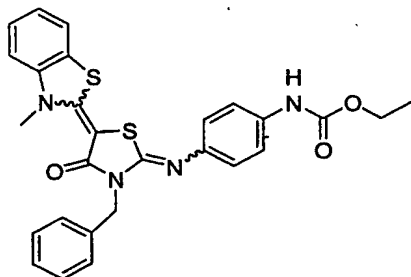
-210-

chromatographed (silica gel, 0-50% EtOAc/Hex) to give the title compound (34 mg, 18%) as a yellow solid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  9.03 (1H, s), 7.50 (2H, d), 7.37 (2H, t), 7.17-7.26 (5H, m), 7.11 (1H, m), 7.05 (1H, t), 6.88 (1H, d), 6.68 (1H, d), 5.03 (2H), 3.60 (3H, s), 3.00 (2H, s), 2.28 (6H, s);  $\text{MS}(\text{ESI})$ : 530( $\text{MH}^+$ ).

5

**EXAMPLE 126**

**Preparation of {4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}carbamic acid ethyl ester**

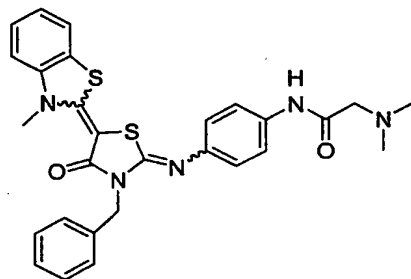


The title compound was prepared from the product of Example 4 in a manner similar to that described in Example 121.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.49 (2H, d), 7.37 (1H, d), 7.20-7.29 (5H, m), 7.07 (1H, t), 6.87-6.95 (3H, m), 6.54 (1H, br s), 5.07 (2H, s), 4.15 (2H, q), 3.61 (3H, s), 1.24 (3H, t);  $\text{MS}(\text{ESI})$ : 517( $\text{MH}^+$ ).

10

**EXAMPLE 127**

**15 Preparation of N-{4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-2-dimethylaminoacetamide**

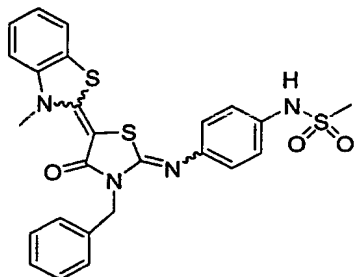


The title compound was prepared from the product of Example 4 in a manner similar to that described in Example 125.  $\text{MS}(\text{ESI})$  530( $\text{MH}^+$ ).

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**EXAMPLE 128**

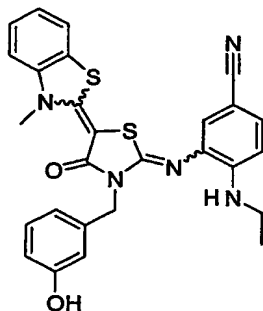
**Preparation of N-{4-[3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}methanesulfonamide**



- 5 The title compound was prepared from the product of Example 4 in a manner similar to that described in Example 120. MS(ESI): 523 (MH<sup>+</sup>).

**EXAMPLE 129**

**Preparation of 4-ethylamino-3-[3-(3-hydroxybenzyl)-5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile**

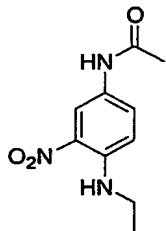


10

- To a N<sub>2</sub>-purged flask was added the product of Example 114 (60 mg, 0.11 mmol) and anhydrous DCM (5 mL). The solution was cooled to -78°C prior to the addition of a 1.0M solution of BBr<sub>3</sub> in DCM (0.50 mL). The solution was allowed to warm to ambient temperature with stirring. After 7h the solution was quenched by addition of MeOH (10 mL) and then concentrated under reduced pressure. The crude material was purified by reverse-phase HPLC (C18 column), eluting with 0.05% TFA in MeCN-H<sub>2</sub>O (1:9 to 9:1) to provide the title compound (15 mg, 26%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.40 (1H, d), 7.35 (1H, t), 7.29 (1H, dd), 7.13-7.25 (3H, m), 6.95-7.01 (3H, m), 6.76 (1H,
- 15

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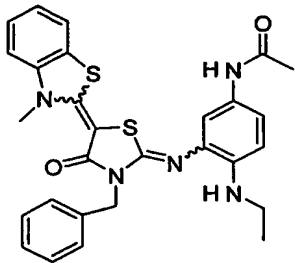
dd), 6.49 (1H, d), 5.08 (2H, s), 3.56 (3H, s), 3.02 (2H, q), 1.05 (3H, t);  
MS(ESI): 514(MH<sup>+</sup>).

**EXAMPLE 130****Preparation of 4'-ethylamino-3'-nitroacetanilide**

5

To a solution of 4-fluoro-3-nitroaniline (2.5 g, 16 mmol) in DCM (35 mL) was added acetic anhydride (2.3 mL, 24 mmol). The solution was stirred 15min, and the resulting off-white precipitates were collected by filtration under reduced pressure. To a solution of the intermediate acetanilide in anhydrous THF (15 mL) was added a 2.0M solution of ethylamine in THF (8.0 mL). The solution was stirred at ambient temperature 14h, and the resulting precipitates were collected by filtration under reduced pressure and dried under vacuum to provide the title compound (2.4 g, 68 %). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.08 (1H, d), 7.90 (1H, br s), 7.78 (1H, dd), 7.32 (1H, br s), 6.82 (1H, d), 3.35 (2H, q), 2.16 (3H, s), 1.36 (3H, t).

15

**B. Preparation of 4-ethylamino-3-[3-(3-fluorobenzyl)-5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile**

In a manner similar to Example 30, intermediate 4'-ethylamino-3'-nitroacetanilide was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium p-toluenesulfonate to afford the title compound. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 9.58 (1H,

20

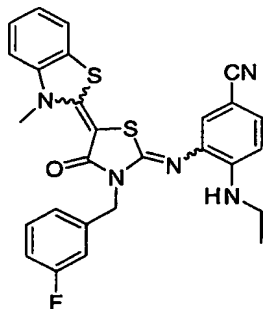


-213-

s), 7.76 (1H, d), 7.18-7.46 (9H, m), 7.12 (1H, d), 6.47 (1H, d), 5.09 (2H, s), 3.82 (1H, br s), 3.79 (3H, s), 2.92 (2H, t), 1.98 (3H, s), 0.97 (3H, t); MS(ESI): 530(MH<sup>+</sup>).

**EXAMPLE 131**

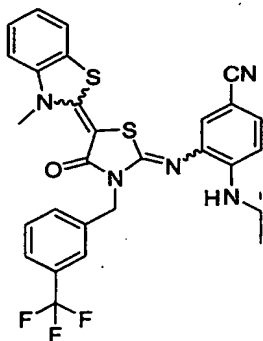
**5 Preparation of 4-ethylamino-3-[3-(3-fluorobenzyl)-5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile**



The title compound was synthesized in a manner similar or to that described in Example 83 by replacing 3-picolyl isothiocyanate hydrobromide with 3-fluorobenzylisothiocyanate. MS(ESI): 516 (MH<sup>+</sup>).

**EXAMPLE 132**

**Preparation of 4-ethylamino-3-[5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxo-3-(3-trifluoromethylbenzyl)thiazolidin-2-ylideneamino]benzonitrile**

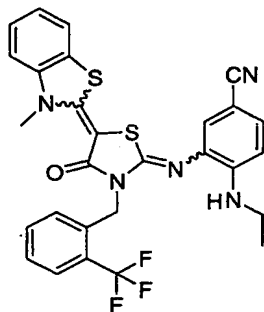


**15** The title compound was synthesized in a manner similar to that described in Example 83 by replacing 3-picolyl isothiocyanate hydrobromide with 3-(trifluoromethyl)benzylisothiocyanate. MS(ESI): 566 (MH<sup>+</sup>).

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**EXAMPLE 133**

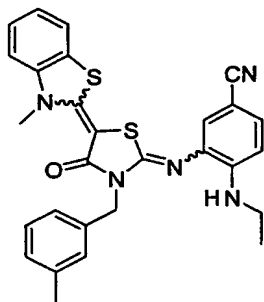
**Preparation of 4-ethylamino-3-[5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-3-(2-trifluoromethylbenzyl)thiazolidin-2-ylideneamino]benzonitrile**



- 5 The title compound was synthesized in a manner similar to that described in Example 83 by replacing 3-picolyl isothiocyanate hydrobromide with 2-(trifluoromethyl)benzylisothiocyanate. MS(ESI): 566 (MH<sup>+</sup>).

**EXAMPLE 134**

- 10 **Preparation of 4-ethylamino-3-[5-(3-methyl-3*H*-benzothiazol-2-ylidene)-3-(3-methylbenzyl)-4-oxothiazolidin-2-ylideneamino]benzonitrile**

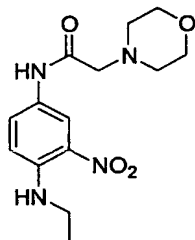


The title compound was prepared in a manner similar to that described in Example 83 by replacing 3-picolyl isothiocyanate hydrobromide with 3-methylbenzylisothiocyanate. MS(ESI): 512(MH<sup>+</sup>).

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## EXAMPLE 135

## A. Preparation of 4'-ethylamino-2-(morpholin-4-yl)-3'-nitroacetanilide

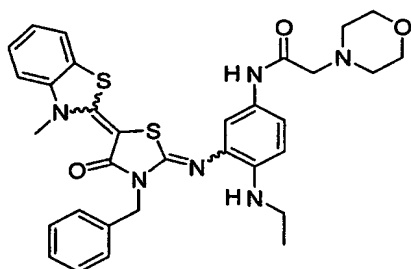


The title compound was synthesized in a manner similar to Example

- 5 130 by replacing acetic anhydride with morpholin-4-ylacetyl chloride hydrochloride. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.94 (1H, s), 8.11 (1H, d), 7.88 (1H, dd), 6.83 (1H, d), 3.78 (4H, t), 3.34 (2H, q), 3.13 (2H, s), 2.62 (4H, t), 1.31 (3H, t).

B. Preparation of N-[3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl]-2-

10 morpholin-4-ylacetamide



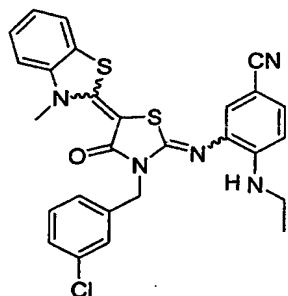
In a manner similar to Example 30, intermediate 4'-ethylamino-2-(morpholin-4-yl)-3'-nitroacetanilide was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-

- 15 thiazolium *p*-toluenesulfonate to afford the title compound. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.87 (1H, s), 7.49-7.53 (3H, m), 7.28-7.37 (5H, m), 7.19 (1H, t), 7.12 (1H, dd), 7.04 (1H, d), 6.57 (1H, d), 5.19 (2H, s), 3.79 (8H, br s), 3.16 (2H, s), 3.01 (2H, q), 2.66 (4H, br s), 1.06 (3H, t); MS(ESI): 615(MH<sup>+</sup>).

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**EXAMPLE 136**

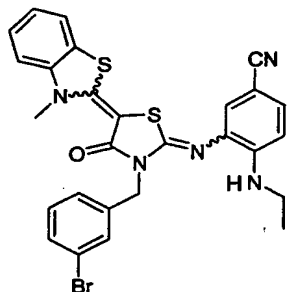
**Preparation of 3-[3-(3-chlorobenzyl)-5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile**



- 5 The title compound was synthesized in a manner similar to that described in Example 83 by replacing 3-picolyl isothiocyanate hydrobromide with 3-chlorobenzylisothiocyanate. MS(ESI): 533 (MH<sup>+</sup>).

**EXAMPLE 137**

- 10 **Preparation of 3-[3-(3-bromobenzyl)-5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile**

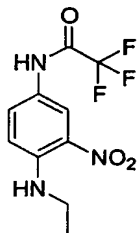


- The title compound was synthesized in a manner similar to that described in Example 83 by replacing 3-picolyl isothiocyanate hydrobromide with 3-bromobenzylisothiocyanate. MS(ESI): 578(MH<sup>+</sup>).

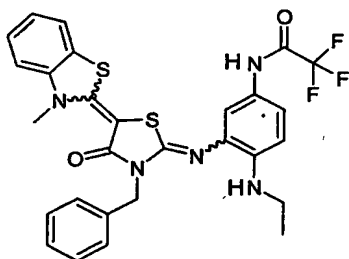
-217-

## EXAMPLE 138

## A. Preparation of 4'-ethylamino-3'-nitro-2,2,2-trifluoroacetanilid



The title compound was prepared in a manner similar to that described  
5 in Example 130 by replacing acetic anhydride with trifluoroacetic anhydride (TFAA). TLC (1:1 Hex/EtOAc)  $R_f$  = 0.5; MS(ESI): 278(MH<sup>+</sup>).

B. Preparation of N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl}-2,2,2-trifluoroacetamide

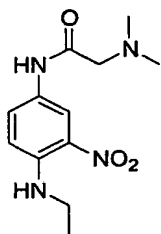
10

In a manner similar to Example 30, intermediate 4'-ethylamino-3'-nitro-  
2,2,2-trifluoroacetanilide was hydrogenated and then condensed with 3-  
benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-  
thiazolium *p*-toluenesulfonate to afford the title compound. MS(ESI):  
15 584(MH<sup>+</sup>).

-218-

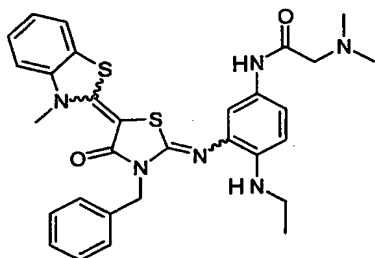
## EXAMPLE 139

## A. Preparation of 2-dimethylamino-4'-ethylamino-3'-nitroacetanilide



- The title compound was prepared in a similar manner as that described in Example 130 by replacing acetic anhydride with N,N-dimethylaminoacetyl chloride hydrochloride. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 9.04 (1H, s), 8.16 (1H, d), 7.95 (1H, dd), 7.89 (1H, br s), 6.84 (1H, d), 3.35 (2H, q), 3.09 (2H, s), 2.39 (6H, s), 1.36 (3H, t); MS(ESI): 267(MH<sup>+</sup>).

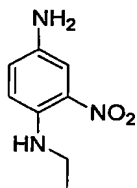
B. Preparation of N-{3-[3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl}-2-dimethylaminoacetamide



- In a manner similar to Example 30, intermediate 2-dimethylamino-4'-ethylamino-3'-nitroacetanilide was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.85 (1H, s), 7.43 (3H, t), 7.18-7.28 (5H, m), 7.10 (2H, t), 6.95 (1H, d), 6.48 (1H, d), 5.10 (2H, s), 3.71 (3H, s), 3.03 (2H, s), 2.93 (2H, q), 2.33 (6H, s), 0.97 (3H, t); MS(ESI): 584(MH<sup>+</sup>).

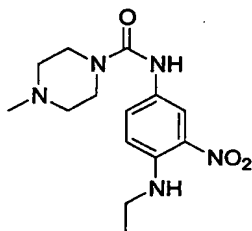
## EXAMPLE 140

## A. Preparation of 4-ethylamino-3-nitroaniline



To a pressure tube was added 4-fluoro-3-nitroaniline (550 mg, 3.50 mmol) and a 2.0 M solution of ethylamine in THF (8 mL). The sealed tube was heated at 120°C for 24h. The reaction solution was cooled, diluted with EtOAc (30 mL), washed with satd NaHCO<sub>3</sub> (2 x 25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure to provide the title compound (625 mg, 98%) as a purple solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.72 (1H, br s), 7.49 (1H, d), 6.96 (1H, dd), 6.74 (1H, d), 3.45 (2H, br s), 3.30 (2H, m), 1.33 (3H, t).

## B. Preparation of 4-methylpiperazine-1-carboxylic acid (4-ethylamino-3-nitro-phenyl)amide

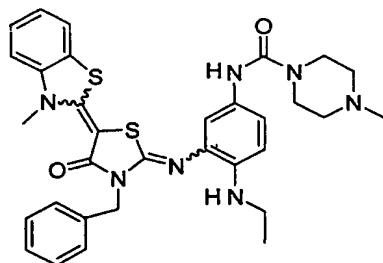


To a 100 mL flask was added 4-ethylamino-3-nitroaniline (625 mg, 3.45 mmol), chloroform (30 mL), and triphosgene (341 mg, 1.15 mmol). To the solution was added satd NaHCO<sub>3</sub> (30 mL), and the biphasic mixture was stirred for 30 min. The organic phase was partitioned, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was dissolved in anhydrous THF (16 mL), and 4-methylpiperazine (291 mg, 2.90 mmol) was added. The solution was stirred at 40°C for 1h, cooled and concentrated under reduced pressure to provide the title compound (1.0 g, 94 %) as a red solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.91 (1H, d), 7.84 (1H, t), 7.61 (1H, dd),

-220-

6.95 (1H, s), 6.73 (1H, d) 3.52 (4H, t), 3.31 (2H, m), 2.42 (4H, t), 2.32 (3H, s), 1.34 (3H, t); MS(ESI): 308(MH<sup>+</sup>).

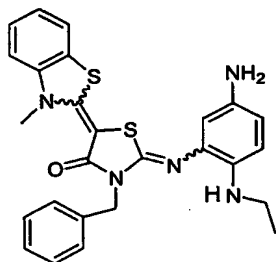
**C. Preparation of 4-methylpiperazine-1-carboxylic acid {3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl}amide**



In a manner similar to Example 30, intermediate 4-methylpiperazine-1-carboxylic acid (4-ethylamino-3-nitro-phenyl)amide was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. MS(ESI): 614(MH<sup>+</sup>).

**EXAMPLE 141**

**Preparation of 2-(5-amino-2-ethylaminophenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one**



To the product of Example 138 (0.15 g, 0.26 mmol) in MeOH (30 mL) was added H<sub>2</sub>O (6 mL) and fine mesh K<sub>2</sub>CO<sub>3</sub> (0.30 g, 1.5 mmol), and the solution was stirred 24h at 55°C. The reaction mixture was cooled, diluted with EtOAc (30 mL), washed with H<sub>2</sub>O (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude material was purified

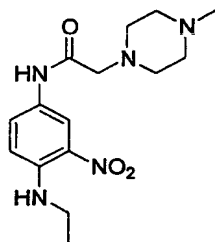


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by reverse-phase HPLC (C18 column), eluting with 0.05% TFA in MeCN-H<sub>2</sub>O (1:9 to 9:1) to provide the title compound (2 mg). MS(ESI): 488(MH<sup>+</sup>).

**EXAMPLE 142**

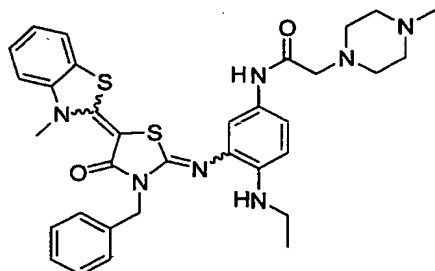
**A. Preparation of 4'-ethylamino-2-(4-methylpiperazin-1-yl)-3'-nitroacetanilide**



- To a 100 mL flask was added 4-fluoro-3-nitroaniline (0.83 g, 5.3 mmol), DCM (30 mL), bromoacetyl chloride (0.53 mL, 6.4 mmol), and TEA (0.74 mL, 5.3 mmol). The reaction solution was stirred at room temperature 2h and then
- 10 quenched with satd NaHCO<sub>3</sub> (20 mL). The organic phase was partitioned, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered under vacuum, and concentrated under reduced pressure. The resulting amide (1.31 g, 4.73 mmol) was added to a 100 mL flask along with MeCN (20 mL), 4-methylpiperazine (0.53 mL, 4.7 mmol), and K<sub>2</sub>CO<sub>3</sub> (655 mg, 4.74 mmol). The reaction slurry was stirred 14h at 35°C prior
- 15 to removal of excess K<sub>2</sub>CO<sub>3</sub> by vacuum filtration. The filtrate was concentrated under reduced pressure, and the crude residue was chromatographed (SiO<sub>2</sub>, hexane/EtOAc) to provide 400 mg of intermediate amide. In a manner similar to that described in Example 31, the intermediate amide was treated with ethylamine to afford the title compound. <sup>1</sup>H-NMR
- 20 (CDCl<sub>3</sub>): δ 9.66 (1H, s), 8.44 (1H, m), 8.05 (1H, m), 7.17 (1H, t), 3.25 (2H, s), 3.19 (4H, m), 3.14 (2H, m), 2.88 (4H, m), 2.53 (3H, 2), 1.38 (3H, t); MS(ESI): 322(MH<sup>+</sup>).

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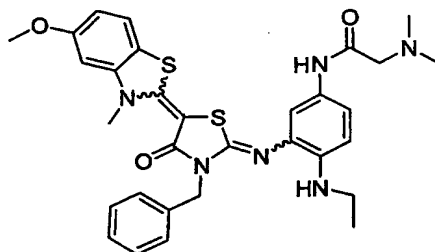
**B. Preparation of N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl}-2-(4-methylpiperazin-1-yl)acetamide**



- 5 In a manner similar to Example 30, intermediate 4'-ethylamino-2-(4-methylpiperazin-1-yl)-3'-nitroacetanilide was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluene sulfonate to afford the title compound. MS(ESI): 628(MH<sup>+</sup>).

10 **EXAMPLE 143**

**Preparation of N-{3-[3-benzyl-5-(5-methoxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl}-2-dimethylaminoacetamide**

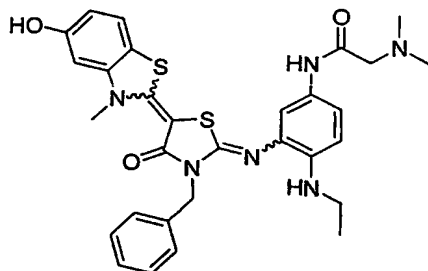


- 15 The title compound was prepared in a manner similar to Example 1 by replacing 2-(methylthio)benzothiazole with 2-mercapto-5-methoxybenzothiazole and by replacing aniline with 3'-amino-2-dimethylamino-4'-ethylaminoacetanilide. MS(ESI): 603(MH<sup>+</sup>).

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**EXAMPLE 144**

**Preparation of N-{3-[3-benzyl-5-(5-hydroxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl}-2-dimethylaminoacetamide**

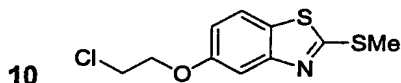


5

The title compound was prepared from the product of Example 143 in a manner similar to that described in Example 129. MS(ESI): 589 (MH<sup>+</sup>).

**EXAMPLE 145**

**A. Preparation of 5-(2-chloroethoxy)-2-methylthio-benzothiazole**



10

To a 250 mL flask was added 2-mercapto-5-methoxybenzothiazole (5.1 g, 26 mmol), MeCN (63 mL), methyl *p*-toluenesulfonate (4.8 g, 26 mmol) and TEA (4.4 mL, 31 mmol). After stirring 16h at ambient temperature, the solution was concentrated under reduced pressure. The crude material was diluted with EtOAc (200 mL), washed with water (2 x 75 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The resulting viscous oil was dissolved in DCM (40 mL), and transferred to an argon-purged 250 mL flask. The solution was cooled to -78°C prior to the addition of a 1.0 M BBr<sub>3</sub> solution in DCM (64 mL). The reaction suspension was allowed to warm to room temperature. After 16h the reaction solution was cooled to -78°C and quenched by addition of MeOH (100 mL). The resulting precipitates were isolated by vacuum filtration to yield 5-hydroxy-2-methylthio-benzothiazole (3.9 g, 76%) as a white solid.

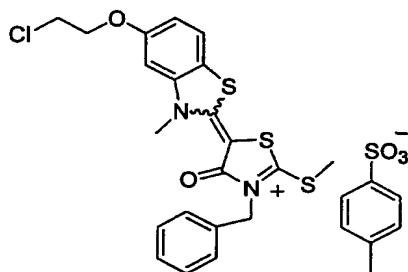
To a solution of 5-hydroxy-2-methylthio-benzothiazole (2.1 g, 11 mmol) in anhydrous DMF (25 mL) was added bromo-2-chloroethane (4.4 mL, 53

25

-224-

mmol) and powdered  $K_2CO_3$  (7.3 g, 53 mmol). The reaction slurry was heated at 70°C for 13h. The slurry was filtered under vacuum and the filtrate was concentrated under reduced pressure. The crude material was chromatographed ( $SiO_2$ , 0-20% EtOAc/Hex) to afford the title compound (1.2 g, 46%).  $^1H$ -NMR ( $CDCl_3$ ):  $\delta$  7.62 (1H, d), 7.39 (1H, d), 6.97 (1H, dd), 4.29 (2H, t), 3.85 (2H, t), 2.79 (3H, s); MS(ESI): 259( $MH^+$ ).

**B. Preparation of 3-benzyl-5-[5-(2-chloroethoxy)-3-methylbenzothiazol-2-ylidene]-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate**

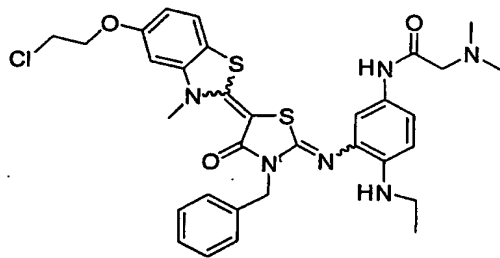


10

The title compound was prepared in a manner similar to that described in Example 1 by replacing 2-(methylthio)benzothiazole with 5-(2-chloroethoxy)-2-methylthio-benzothiazole.  $^1H$ -NMR ( $DMSO-d_6$ ):  $\delta$  8.08 (1H, d), 7.65 (1H, d), 7.36-7.53 (7H, m), 7.22 (1H, dd), 7.09 (1H, d), 5.38 (2H, s), 4.45 (2H, t), 4.25 (3H, s), 4.03 (2H, t), 3.01 (3H, s), 2.28 (3H, s) MS(ESI): 463 ( $M^+ - p$ -toluenesulfonate).

15

**C. Preparation of N-(3-{3-benzyl-5-[5-(2-chloroethoxy)-3-methyl-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylamino-phenyl)-2-dimethylaminoacetamide**



20

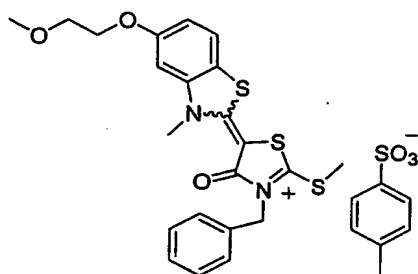
-225-

In a manner similar to Example 30, intermediate 2-dimethylamino-4'-ethylamino-3'-nitroacetanilide was hydrogenated and then condensed with 3-benzyl-5-[5-(2-chloroethoxy)-3-methylbenzothiazol-2-ylidene]-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. MS(ESI):

5 651(MH<sup>+</sup>).

#### EXAMPLE 146

##### A. Preparation of 3-benzyl-5-[5-(2-methoxyethoxy)-3-methylbenzothiazol-2-ylidene]-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate

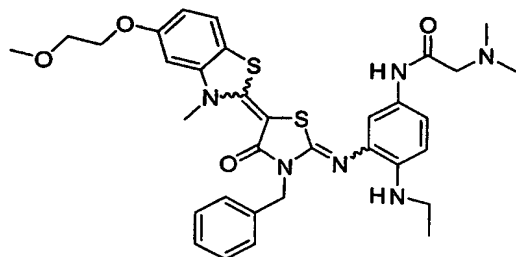


10

The title compound was synthesized in a manner similar to that described in Example 145 by replacing bromo-2-chloroethane with 2-chloroethyl methylether. MS(ESI): 459 (M<sup>+</sup> - *p*-toluenesulfonate).

##### B. Preparation of N-(3-{3-benzyl-5-[5-(2-methoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylamino-phenyl)-2-dimethylaminoacetamide

15



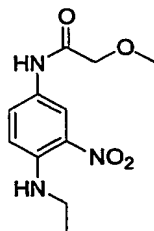
In a manner similar to Example 30, intermediate 2-dimethylamino-4'-ethylamino-3'-nitroacetanilide was hydrogenated and then condensed with 3-benzyl-5-[5-(2-methoxyethoxy)-3-methylbenzothiazol-2-ylidene]-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. <sup>1</sup>H-NMR

20

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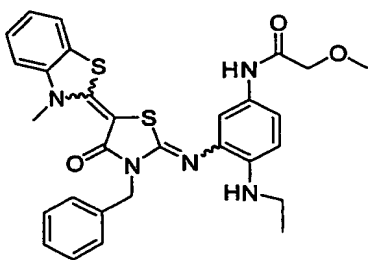
(CDCl<sub>3</sub>):  $\delta$  9.08 (1H, s), 7.46 (2H, d), 7.27-7.35 (5H, m), 7.16 (1H, dd), 6.69 (1H, dd), 6.62 (1H, d), 6.51 (1H, d), 5.14 (2H, s), 4.13 (2H, t), 3.75 (2H, t), 3.71 (2H, s), 3.44 (3H, s), 3.19 (2H, s), 2.94 (2H, q), 2.46 (6H, s), 1.02 (3H, t); MS(ESI): 647(MH<sup>+</sup>).

5

**EXAMPLE 147****A. Preparation of 4'-ethylamino-2-methoxy-3'-nitroacetanilide**

The title compound was prepared in a similar manner as that described in Example 130 by replacing acetic anhydride with methoxyacetyl chloride.

10 <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta$  8.20 (1H, d), 8.17 (1H, br s), 7.88 (1H, dd), 6.68 (1H, d), 4.03 (2H, s), 3.52 (3H, s), 3.37 (2H, q), 1.62 (2H, br s), 1.38 (3H, t).

**B. Preparation of N-{3-[3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl}-2-methoxyacetamide**

15

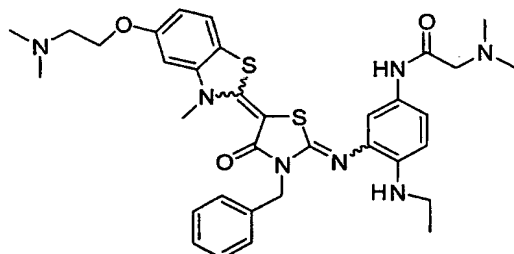
In a manner similar to Example 30, intermediate 4'-ethylamino-2-methoxy-3'-nitroacetanilide was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. <sup>1</sup>H-NMR (CDCl<sub>3</sub>):

20  $\delta$  7.99 (1H, s), 7.39-7.44 (3H, m), 7.17-7.28 (5H, m), 7.05-7.11 (2H, m), 6.94 (1H, d), 6.50 (1H, d), 5.08 (2H, s), 3.92 (2H, s), 3.66 (3H, s), 3.41 (3H, s), 2.91 (2H, q), 0.96 (3H, t); MS(ESI): 560(MH<sup>+</sup>).

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**EXAMPLE 148**

**Preparation of N-(3-{3-benzyl-5-[5-(2-dimethylaminoethoxy)-3-methyl-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminophenyl)-2-dimethylaminoacetamide**



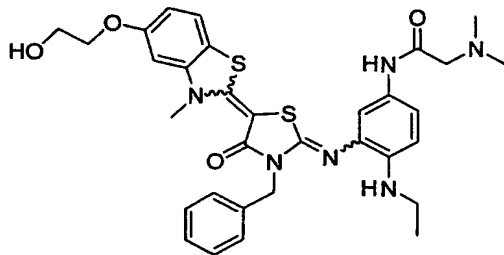
5

To a pressure tube was added the product of Example 145 (150 mg, 0.23 mmol), tetra-*n*-butylammonium iodide (85 mg, 0.23 mmol), and 2.0 M solution of dimethylamine in THF (6 mL). The tube was sealed and heated at 65°C for 14h. The solution was cooled and concentrated under reduced pressure, and the crude material was purified by chromatography (silica gel, 0-20% MeOH/DCM) to provide the title compound (30 mg, 20%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.83 (1H, s), 7.45 (2H, d), 7.22-7.34 (5H, m), 7.11 (1H, dd), 6.71 (1H, dd), 6.63 (1H, d), 6.52 (1H, d), 5.14 (2H, s), 4.12 (2H, t), 3.70 (3H, s), 3.04 (2H, s), 2.97 (2H, q), 2.82 (2H, t), 2.40 (6H, s), 2.35 (6H, s), 1.02 (3H, t); MS(ESI): 660(MH<sup>+</sup>).

15

**EXAMPLE 149**

**Preparation of N-(3-{3-benzyl-5-[5-(2-hydroxyethoxy)-3-methyl-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminophenyl)-2-dimethylaminoacetamide**

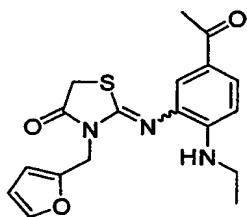


20

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To an 8 mL vial was added the product of Example 145 (100 mg, 0.15 mmol), anhydrous DMF (5 mL), and tetra-n-butylammonium iodide (570 mg, 1.54 mmol). The solution was heated at 75°C for 4h prior to the addition of sodium acetate (250 mg, 3.08 mmol). The reaction solution was then heated  
5 16h at 75°C. To the solution was added MeOH (2 mL), 5M aqueous NaOH (1 mL) and H<sub>2</sub>O (1 mL). After heating at 50°C for 5h, the reaction mixture was cooled, neutralized with conc HCl and concentrated under reduced pressure. The residue was taken up into DCM (50 mL), and the organic phase was washed with water (2 x 25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated  
10 under reduced pressure. The crude material was chromatographed (SiO<sub>2</sub>, 0-10% MeOH/DCM) to provide the title compound (5 mg, 5%). <sup>1</sup>H NMR (MeOH-d<sub>4</sub>): δ 8.92 (1H, s), 7.11-7.26 (7H, m), 6.97 (1H, dd), 6.66 (1H, dd), 6.60 (1H, d), 6.44 (1H, d), 5.01 (2H, s), 3.96 (2H, t), 3.77 (2H, t), 3.62 (3H, s), 3.00 (2H, s), 2.82 (2H, q), 2.28 (6H, s), 0.89 (3H, t); MS(ESI) 633(MH<sup>+</sup>).

15

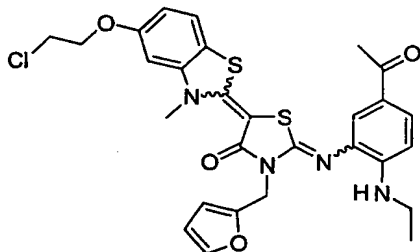
**EXAMPLE 150****A. Preparation of 2-(5-acetyl-2-ethylaminophenylimino)-3-furan-2-ylmethyl-thiazolidin-4-one**

The title compound was prepared from furfuryl isothiocyanate and 3'-amino-4'-(ethylamino)acetophenone in a manner similar to that described in  
20 Example 52. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.73 (1H, dd), 7.61 (1H, s), 7.38 (1H, s), 6.59 (1H, d), 6.43 (1H, d), 6.36 (1H, m), 5.06 (2H, s), 3.88 (2H, s), 3.21 (2H, q), 2.50 (3H, s), 1.27 (3H, t); MS(ESI): 358 (MH<sup>+</sup>).



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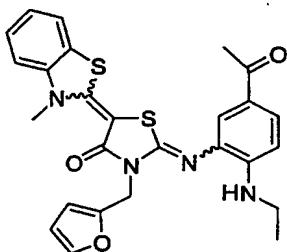
**B. Preparation of 2-(5-acetyl-2-ethylaminophenylimino)-5-[5-(2-chloroethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-3-furan-2-ylmethylthiazolidin-4-one**



- 5 In a manner similar to Example 45, intermediate 5-(2-chloroethoxy)-2-(methylthio)benzothiazole was alkylated with methyl *p*-toluenesulfonate and then condensed with the above 2-(5-acetyl-2-ethylaminophenylimino)-3-furan-2-ylmethyl-thiazolidin-4-one. MS(ESI): 583 (MH<sup>+</sup>).

**EXAMPLE 151**

- 10 **Preparation of 2-(5-acetyl-2-ethylaminophenylimino)-3-furan-2-ylmethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one**

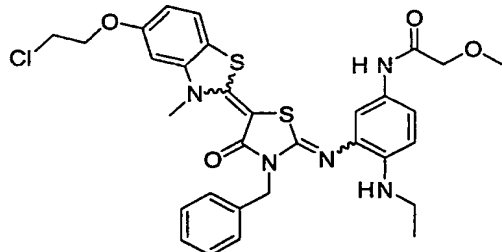


- The title compound was synthesized in a manner similar to that described in Example 82 by replacing 3-picoly isothiocyanate hydrobromide with 2-furfuryl isothiocyanate. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.70-7.74 (2H, m), 7.52 (1H, d), 7.33-7.39 (2H, m), 7.20 (1H, t), 7.06 (1H, d), 6.68 (1H, d), 6.50 (1H, d), 6.35 (1H, m), 5.24 (2H, s), 3.76 (3H, s), 3.23 (2H, q), 2.49 (3H, s), 1.28 (3H, t); MS(ESI): 505 (MH<sup>+</sup>).

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**EXAMPLE 152**

**Preparation of N-(3-{3-benzyl-5-[5-(2-chloroethoxy)-3-methyl-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminophenyl)-2-methoxyacetamide**

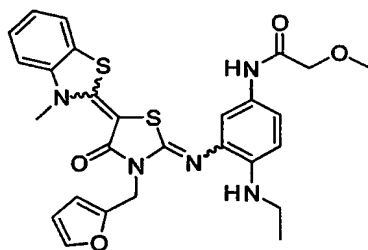


5

In a manner similar to Example 30, intermediate 4'-ethylamino-2-methoxy-3'-nitroacetanilide was hydrogenated and then condensed with 3-benzyl-5-[5-(2-chloroethoxy)-3-methylbenzothiazol-2-ylidene]-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. MS(ESI):

10 638(MH<sup>+</sup>).**EXAMPLE 153**

**Preparation of N-(4-ethylamino-3-[3-furan-2-ylmethyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl)-2-methoxyacetamide**



15

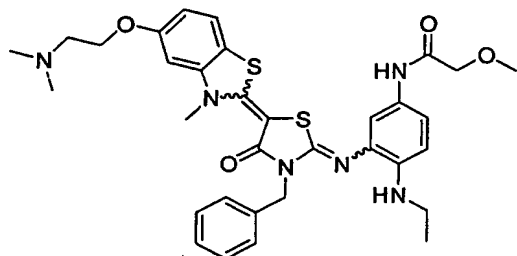
The title compound was prepared in a manner similar to that described in Example 84 by replacing 3-amino-4-(ethylamino)benzonitrile with 3'-amino-4'-ethylamino-2-methoxyacetanilide. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.07 (1H, s), 7.50 (1H, dd), 7.37 (1H, d), 7.29-7.34 (2H, m), 7.16 (2H, m), 7.02 (1H, d), 6.66 (1H, br s), 6.45 (1H, d), 6.32 (1H, m), 5.15 (2H, s), 3.99 (2H, s), 3.75 (3H, s), 3.51 (3H, s), 3.13 (2H, q), 1.23 (3H, t); MS(ESI): 550 (MH<sup>+</sup>).

20

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## EXAMPLE 154

Preparation of N-(3-{3-benzyl-5-[5-(2-dimethylaminoethoxy)-3-methyl-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminophenyl)-2-methoxyacetamide



5

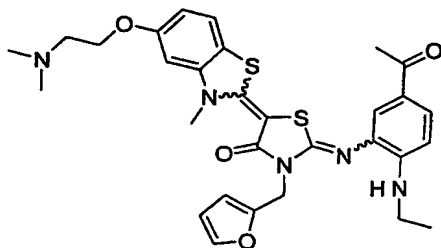
The title compound was prepared from the product of Example 152 in a manner similar to that described in Example 148. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.03 (1H, s), 7.48 (2H, d), 7.24-7.37 (5H, m), 7.14 (1H, dd), 6.74 (1H, dd), 6.65 (1H, d), 6.53 (1H, d), 5.16 (2H, s), 4.13 (2H, t), 4.00 (2H, s), 3.72 (3H, s), 3.48 (3H, s), 2.99 (2H, q), 2.81 (2H, t), 2.39 (6H, s), 1.03 (3H, t); MS(ESI): 647(MH<sup>+</sup>).

10

## EXAMPLE 155

Preparation of 2-(5-acetyl-2-ethylaminophenylimino)-5-[5-(2-dimethylaminoethoxy)-3-methyl-3H-benzothiazol-2-ylidene]-3-furan-2-ylmethylthiazolidin-4-one

15

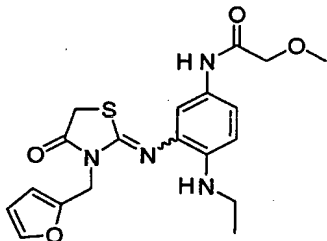


The title compound was prepared from the product of Example 150 in a manner similar to that described in Example 148. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.67-7.72 (2H, m), 7.37 (1H, s), 7.35 (1H, d), 6.76 (1H, dd), 6.64 (1H, d), 6.57 (1H, d), 6.45 (1H, d), 6.34 (1H, dd), 5.18 (2H, s), 4.89 (1H, t), 4.10 (2H, t), 3.71 (3H, s), 3.22 (2H, m), 2.75 (2H, m), 2.51 (3H, s), 2.35 (6H, s), 0.97 (3H, t); MS(ESI): 592(MH<sup>+</sup>).

20

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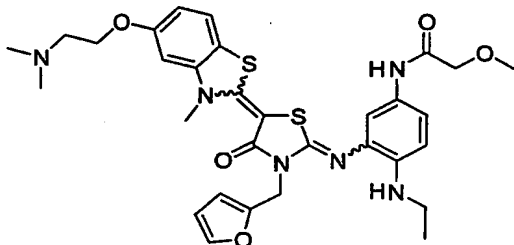
## EXAMPLE 156

**A. Preparation of N-[4-ethylamino-3-(3-furan-2-ylmethyl-4-oxothiazolidin-2-ylideneamino)phenyl]-2-methoxyacetamide**

5       The title compound was synthesized from 2-furfuryl isothiocyanate and 3'-amino-4'-ethylamino-2-methoxyacetanilide in a manner similar to that described in Example 52. MS(ESI): 403 (MH<sup>+</sup>).

**B. Preparation of N-(3-{5-[5-(2-dimethylaminoethoxy)-3-methyl-3H-benzothiazol-2-ylidene]-3-furan-2-ylmethyl-4-oxothiazolidin-2-ylideneamino}-4-ethylaminophenyl)-2-methoxyacetamide**

10



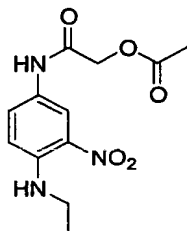
In a manner similar to Example 45, intermediate 5-(2-chloroethoxy)-2-(methylthio)benzothiazole was alkylated with methyl *p*-toluenesulfonate and then condensed with the above N-[4-ethylamino-3-(3-furan-2-ylmethyl-4-oxothiazolidin-2-ylideneamino)phenyl]-2-methoxyacetamide. The resulting product was transformed into the title compound following the procedure outlined in Example 148. MS(ESI): 583 (MH<sup>+</sup>).

15

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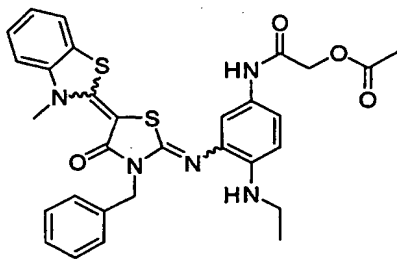
## EXAMPLE 157

## A. Preparation of 2-acetoxy-4'-ethylamino-3'-nitroacetanilide



To a 100 mL flask was added 4-ethylamino-3-nitroaniline (1.1 g, 6.3 mmol) and anhydrous  $\text{CHCl}_3$  (45 mL). The solution was cooled to  $0^\circ\text{C}$  prior to the addition of bromoacetyl chloride (0.62 mL, 7.5 mmol) and TEA (1.7 mL, 13 mmol) under a nitrogen atmosphere. The reaction mixture was allowed to warm to ambient temperature over 1h before the solvent was removed under reduced pressure. The crude material was chromatographed ( $\text{SiO}_2$ , 0-40% EtOAc/Hex) to provide the intermediate acetanilide (540 mg, 1.8 mmol) as a red solid. To a solution of the intermediate in anhydrous DMF (25 mL) was added sodium acetate (1.41 g, 17.2 mmol). The suspension was heated at  $100^\circ\text{C}$  for 4h. After cooling, the reaction mixture was diluted with EtOAc (25 mL), and the excess sodium acetate was removed by filtration under reduced pressure. The filtrate was concentrated under reduced pressure to provide the title compound (420 mg).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.13 (1H, br s), 8.11 (1H, d), 7.90 (1H, br s), 7.79 (1H, dd), 6.80 (1H, d), 4.68 (2H, s), 3.33 (2H, m), 2.21 (3H, s), 1.35 (3H, t); MS(ESI): 282 ( $\text{MH}^+$ ).

B. Preparation of acetic acid {3-[3-benzyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenylcarbamoyl}methyl ester

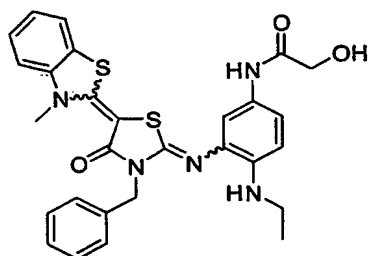


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In a manner similar to Example 30, intermediate 2-acetoxy-4'-ethylamino-3'-nitroacetanilide was hydrogenated and then condensed with 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford the title compound. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.73 (1H, br s), 7.44-7.51 (3H, m), 7.23-7.34 (5H, m), 7.16 (1H, t), 7.08 (1H, dd), 7.00 (1H, d), 6.56 (1H, d), 5.15 (2H, s), 4.67 (2H, s), 3.74 (3H, s), 2.98 (2H, q), 2.20 (3H, s), 1.00 (3H, t); MS(ESI): 588(MH<sup>+</sup>).

**EXAMPLE 158**

**Preparation of N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl}-2-hydroxyacetamide**

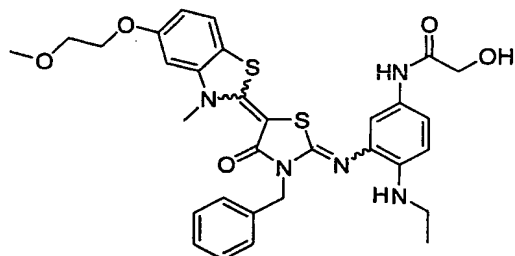


To a 50 mL flask was added the product of Example 157 (0.19 g, 0.32 mmol), CHCl<sub>3</sub> (5 mL), MeOH (10 mL), water (2 mL), and potassium carbonate (0.22 g, 1.6 mmol). After 4h the reaction mixture was diluted with CHCl<sub>3</sub> (40 mL), and the organic phase was partitioned, washed with water (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude sample was chromatographed (silica gel, 0-10% MeOH/DCM) to afford the title compound (37 mg, 21%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.14 (1H, s), 7.42-7.48 (3H, m), 7.27-7.33 (5H, m), 7.15 (1H, t), 7.09 (1H, dd), 6.99 (1H, d), 6.56 (1H, d), 5.15 (2H, s), 4.14 (2H, s), 3.71 (3H, s), 2.95 (2H, q), 0.99 (3H, t); MS(ESI): 546(MH<sup>+</sup>).

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## EXAMPLE 159

**Preparation of N-(3-{3-benzyl-5-[5-(2-methoxyethoxy)-3-methyl-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminophenyl)-2-hydroxyacetamide**



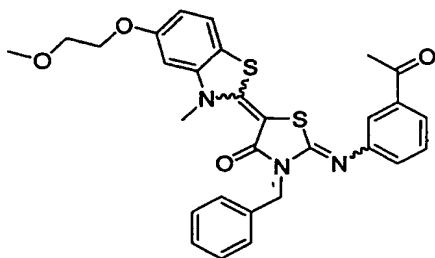
5

In a manner similar to Example 30, intermediate 2-acetoxy-4'-ethylamino-3'-nitroacetanilide was hydrogenated and then condensed with 3-benzyl-5-[5-(2-methoxyethoxy)-3-methylbenzothiazol-2-ylidene]-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate to afford an intermediate thiazolidinone, which was hydrolyzed in a manner similar to Example 158 to provide the title compound. MS(ESI): 620(MH<sup>+</sup>).

10

## EXAMPLE 160

**Preparation of 2-(3-acetylphenylimino)-3-benzyl-5-[5-(2-methoxyethoxy)-3-methyl-3H-benzothiazol-2-ylidene]thiazolidin-4-one**



15

The title compound was synthesized in a manner similar to that described in Example 146 by condensing 3'-aminoacetophenone with 3-benzyl-5-[5-(2-methoxyethoxy)-3-methylbenzothiazol-2-ylidene]-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.75 (1H, d), 7.60-7.64 (3H, m), 7.28-7.50 (6H, m), 7.24 (1H, d), 6.85 (1H, m), 5.21 (2H, s), 4.18

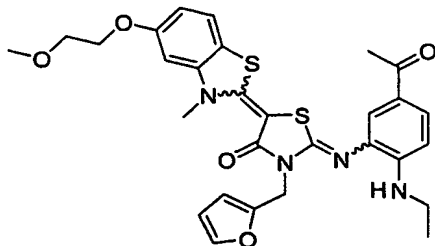
20

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(2H, m), 3.80 (2H, m), 3.70 (3H, s), 3.48 (3H, s), 2.65 (3H, s); MS(ESI): 546(MH<sup>+</sup>).

**EXAMPLE 161**

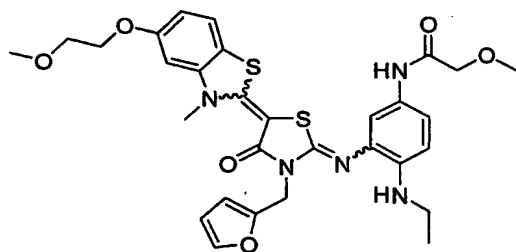
**Preparation of 2-(5-acetyl-2-ethylaminophenylimino)-3-furan-2-ylmethyl-5-[5-(2-methoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]thiazolidin-4-one**



The title compound was prepared in a manner similar to that described in Example 150 by replacing 5-(2-chloroethoxy)-2-(methylthio)benzothiazole with 5-(2-methoxyethoxy)-2-(methylthio)benzothiazole. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.69 (1H, dd), 7.66 (1H, d), 7.34-7.37 (2H, m), 6.76 (1H, dd), 6.65 (1H, d), 6.59 (1H, d), 6.45 (1H, d), 6.33 (1H, m), 5.18 (2H, s), 4.14 (2H, m), 3.75 (2H, m), 3.70 (3H, s), 3.44 (3H, s), 3.20 (2H, q), 2.51 (3H, s), 1.26 (3H, t); MS(ESI): 579(MH<sup>+</sup>).

**EXAMPLE 162**

**Preparation of N-(4-ethylamino-3-{3-furan-2-ylmethyl-5-[5-(2-methoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}phenyl)-2-methoxyacetamide**



In a manner similar to Example 156, 5-(2-methoxyethoxy)-2-(methylthio)benzothiazole was alkylated with methyl *p*-toluenesulfonate and then condensed with intermediate N-[4-ethylamino-3-(3-furan-2-ylmethyl-4-

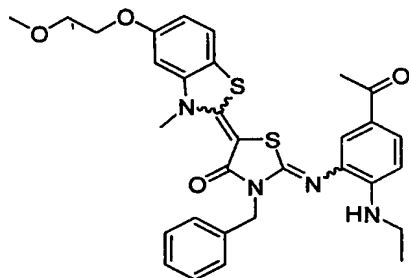


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- oxothiazolidin-2-ylideneamino)phenyl]-2-methoxyacetamide.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.09 (1H, s), 7.28-7.38 (3H, m), 7.15 (1H, dd), 6.76 (1H, dd), 6.64 (1H, d), 6.44 (1H, d), 6.33 (1H, m), 5.16 (2H, s), 4.14 (2H, m), 4.01 (2H, s), 3.77 (2H, m), 3.72 (3H, s), 3.51 (3H, s), 3.44 (3H, s), 3.15 (2H, q), 1.23 (3H, t);
- 5 MS(ESI): 624( $\text{MH}^+$ ).

**EXAMPLE 163**

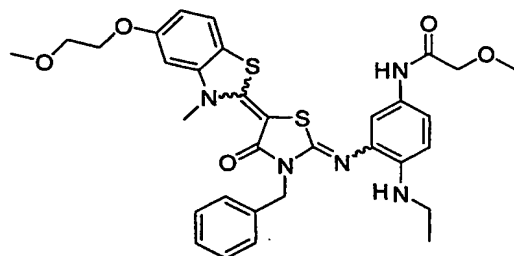
**Preparation of 2-(5-acetyl-2-ethylaminophenylimino)-3-benzyl-5-[5-(2-methoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]thiazolidin-4-one**



- 10 The title compound was synthesized in a manner similar to that described in Example 146 by condensing 3'-amino-4'-(ethylamino)acetophenone with 3-benzyl-5-[5-(2-methoxyethoxy)-3-methylbenzothiazol-2-ylidene]-2-methylthio-4-oxo-2-thiazolium *p*-toluenesulfonate. MS(ESI): 546( $\text{MH}^+$ ).

**EXAMPLE 164**

**Preparation of N-(3-{3-benzyl-5-[5-(2-methoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminophenyl)-2-methoxyacetamide**



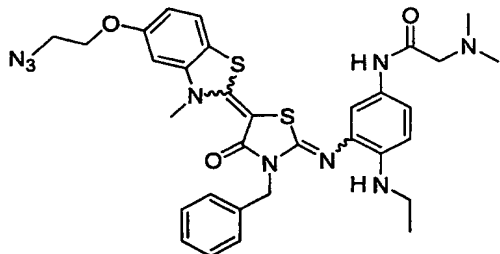
- 20 The title compound was synthesized in a manner similar to that described in Example 146 by replacing 2-dimethylamino-4'-ethylamino-3'-

-238-

nitroacetanilide with 4'-ethylamino-2-methoxy-3'-nitroacetanilide. MS(ESI): 634(MH<sup>+</sup>).

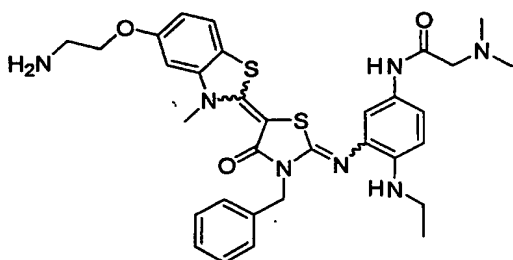
### EXAMPLE 165

- A. Preparation of N-(3-{5-[5-(2-azidoethoxy)-3-methyl-3H-benzothiazol-2-ylidene]-3-benzyl-4-oxothiazolidin-2-ylideneamino}-4-ethylaminophenyl)-2-dimethylaminoacetamide**



- To a 50 mL flask was added the product of Example 145 (225 mg, 345  $\mu$ mol), anhydrous DMF (8mL), sodium azide (112 mg, 1.73 mmol), and sodium iodide (15 mg, 103  $\mu$ mol). The reaction slurry was heated at 70 °C for 6h under N<sub>2</sub>. The reaction mixture was diluted with EtOAc (70 mL), washed with H<sub>2</sub>O (2 x 30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to provide the title compound. MS(ESI): 658(MH<sup>+</sup>).

- B. Preparation of N-(3-{5-[5-(2-aminoethoxy)-3-methyl-3H-benzothiazol-2-ylidene]-3-benzyl-4-oxothiazolidin-2-ylideneamino}-4-ethylaminophenyl)-2-dimethylaminoacetamide**



- To a solution of the above N-(3-{5-[5-(2-azidoethoxy)-3-methyl-3H-benzothiazol-2-ylidene]-3-benzyl-4-oxothiazolidin-2-ylideneamino}-4-ethylamino-phenyl)-2-dimethylaminoacetamide (0.34 mmol) in THF (13 mL) was added triphenylphosphine (100 mg, 380 mmol) and H<sub>2</sub>O (20 mL). The

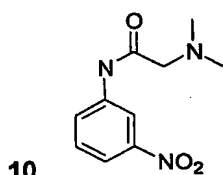
-239-

solution was stirred 48h at room temperature. The solvent was removed under reduced pressure, and the crude material was chromatographed (silica gel, 0-5% MeOH/DCM) to afford the title compound (157 mg, 72% overall).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.85 (1H, s), 7.48 (2H, d), 7.27-7.37 (5H, m), 7.13 (1H, dd), 6.74 (1H, dd), 6.60 (1H, d), 6.55 (1H, d), 5.17 (2H, s), 4.03 (2H, t), 3.73 (3H, s), 3.11 (2H, t), 3.06 (2H, s), 3.00 (2H, q), 2.37 (6H, s), 1.39 (2H, t), 1.04 (3H, t); MS(ESI): 631(MH<sup>+</sup>).

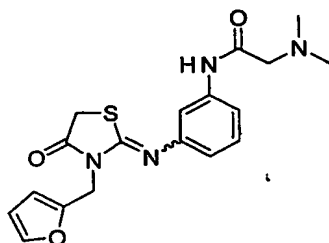
#### EXAMPLE 166

##### A. Preparation of 2-dimethylamino-3'-nitroacetanilide



The title compound was prepared from 3-nitroaniline in a manner similar to that described in Example 139. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 9.04 (1H, br s), 8.39 (1H, t), 8.06 (1H, dd), 7.96 (1H, dd), 7.50 (1H, t), 3.13 (2H, s), 2.41 (6H, s).

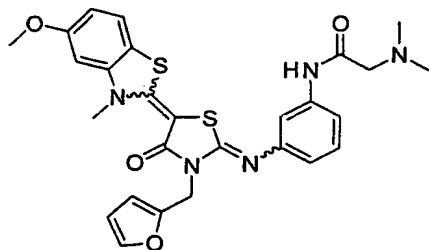
##### 15 B. Preparation of 2-dimethylamino-N-[3-(3-furan-2-ylmethyl-4-oxothiazolidin-2-ylideneamino)phenyl]acetamide



In a manner similar to that described in Example 52, the title compound was prepared from 2-furfuryl isothiocyanate and 3'-amino-2-(dimethylamino)acetanilide, derived from 2-dimethylamino-3'-nitroacetanilide. MS(ESI): 373(MH<sup>+</sup>).

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**C. Preparation of 2-dimethylamino-N-[3-[3-furan-2-ylmethyl-5-(5-methoxy-3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-phenyl]acetamide**

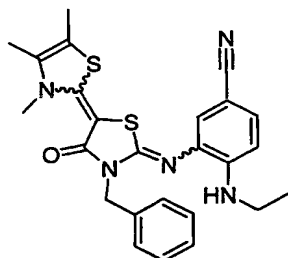


- 5** In a manner similar to Example 45, 2-mercapto-5-methoxybenzothiazole was alkylated with methyl *p*-toluenesulfonate and then condensed with 2-dimethylamino-N-[3-(3-furan-2-ylmethyl-4-oxothiazolidin-2-ylideneamino)-phenyl]acetamide. MS(ESI): 550 (MH<sup>+</sup>).

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**EXAMPLE 167**

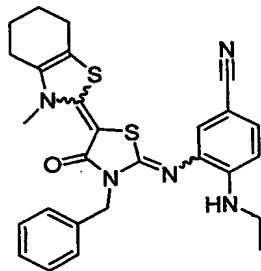
**Preparation of 3-(3'-benzyl-3,4,5-trimethyl-4'-oxo-3',4'-dihydro-3H-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile**



- 5 The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 3-chloro-2-butanone. MS(ESI): 476 (MH<sup>+</sup>).

**EXAMPLE 168**

- 10 **Preparation of 3-[3-benzyl-5-(3-methyl-4,5,6,7-tetrahydro-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile**

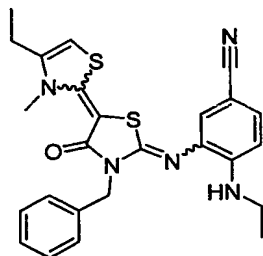


- 15 The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-chlorocyclohexanone. MS(ESI): 502 (MH<sup>+</sup>).

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**EXAMPLE 169**

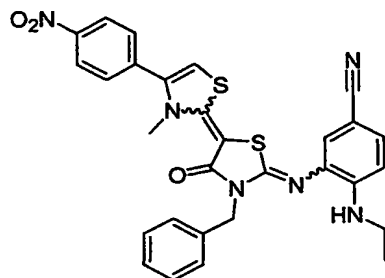
**Preparation of 3-(3'-benzyl-4-ethyl-3-methyl-4'-oxo-3',4'-dihydro-3H-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile**



- 5      The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 1-bromo-2-butanone. MS(ESI): 476 (MH<sup>+</sup>).

**EXAMPLE 170**

- 10      **Preparation of 3-[3'-benzyl-3-methyl-4-(4-nitrophenyl)-4'-oxo-3',4'-dihydro-3H-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile**

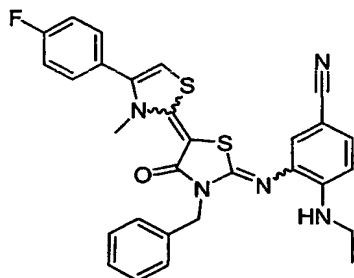


- 15      The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-4'-nitroacetophenone. MS(ESI): 569 (MH<sup>+</sup>).

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## EXAMPLE 171

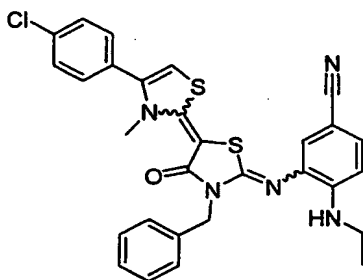
Preparation of 3-[3'-benzyl-4-(4-fluorophenyl)-3-methyl-4'-oxo-3',4'-dihydro-3H-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile



The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-4'-fluoroacetophenone. MS(ESI): 542 (MH<sup>+</sup>).

## EXAMPLE 172

10 Preparation of 3-[3'-benzyl-4-(4-chlorophenyl)-3-methyl-4'-oxo-3',4'-dihydro-3H-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile

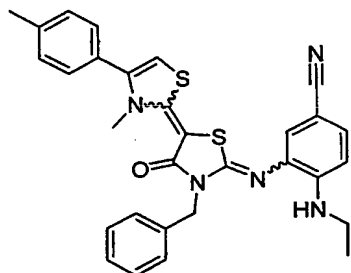


The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-4'-chloroacetophenone. MS(ESI): 558 (MH<sup>+</sup>).

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**EXAMPLE 173**

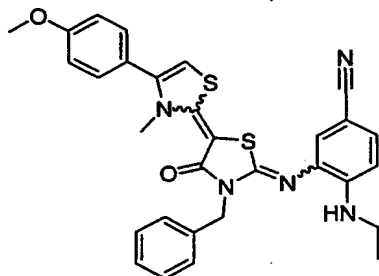
**Preparation of 3-(3'-benzyl-3-methyl-4'-oxo-4-p-tolyl-3',4'-dihydro-3H-[2,5]bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile**



- 5        The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-4'-methylacetophenone. MS(ESI): 538 (MH<sup>+</sup>).

**EXAMPLE 174**

- 10      **Preparation of 3-[3'-benzyl-4-(4-methoxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3H-[2,5]bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile**



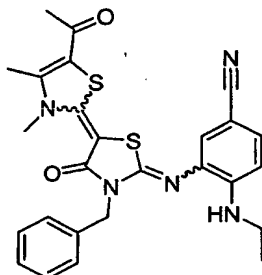
- 15      The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-4'-methoxyacetophenone. MS(ESI): 554 (MH<sup>+</sup>).



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**EXAMPLE 175**

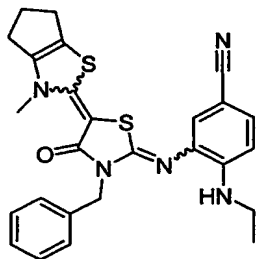
**Preparation of 3-(5-acetyl-3'-benzyl-3,4-dimethyl-4'-oxo-3',4'-dihydro-3H-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile**



- 5        The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 3-chloro-2,4-pentanedione. MS(ESI): 504 (MH<sup>+</sup>).

**EXAMPLE 176**

- 10      **Preparation of 3-[3-benzyl-5-(3-methyl-3,4,5,6-tetrahydrocyclopentathiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile**

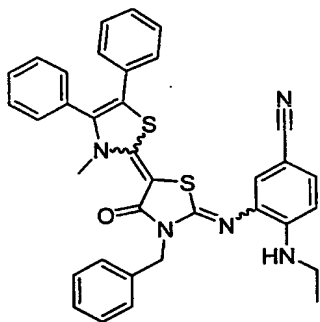


- 15      The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-chlorocyclopentanone. MS(ESI): 488 (MH<sup>+</sup>).

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**EXAMPLE 177**

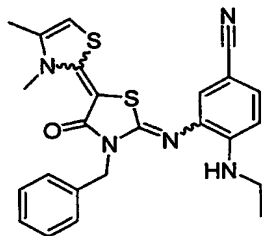
**Preparation of 3-(3'-benzyl-3-methyl-4'-oxo-4,5-diphenyl-3',4'-dihydro-3H-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile**



- 5 The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-chloro-2-phenylacetophenone. MS(ESI): 600 (MH<sup>+</sup>).

**EXAMPLE 178**

- 10 **Preparation of 3-(3'-benzyl-3,4-dimethyl-4'-oxo-3',4'-dihydro-3H-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile**

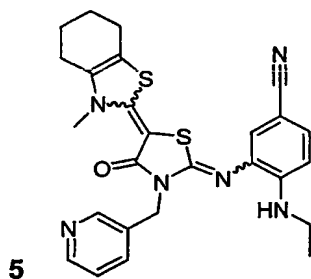


The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with chloroacetone. MS(ESI): 462 (MH<sup>+</sup>).

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## EXAMPLE 179

Preparation of 4-ethylamino-3-[5-(3-methyl-4,5,6,7-tetrahydro-3H-benzothiazol-2-ylidene)-4-oxo-3-pyridin-3-ylmethylthiazolidin-2-ylideneamino]benzonitrile

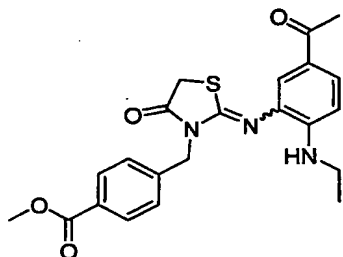


The title compound was prepared in a manner similar to Example 168 by condensing intermediate 3-methyl-2-methylthio-4,5,6,7-tetrahydro-benzothiazol-3-ium *p*-toluenesulfonate with 4-ethylamino-3-(4-oxo-3-pyridin-3-ylmethylthiazolidin-2-ylideneamino)benzonitrile. MS(ESI): 503 (MH<sup>+</sup>).

10

## EXAMPLE 180

A. Preparation of methyl 4-[2-(5-acetyl-2-ethylaminophenylimino)-4-oxothiazolidin-3-ylmethyl]benzoate

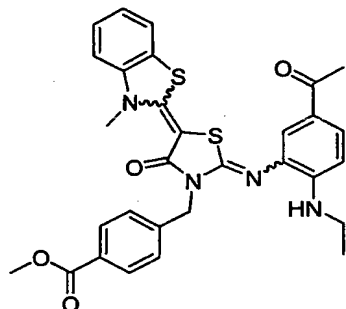


In a manner similar to Example 52, the title compound was prepared from 3'-amino-4'-ethylaminoacetophenone and methyl 4-(isothiocyanatomethyl)benzoate—generated from methyl 4-(aminomethyl)benzoate hydrochloride and thiophosgene. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.04 (2H, d), 7.69 (1H, m), 7.58 (1H, s), 7.47 (2H, d), 6.52 (1H, d), 5.10 (2H, s), 3.96 (2H, s), 3.92 (3H, s), 3.05 (2H, q), 2.49 (3H, s), 1.03 (3H, t).

15

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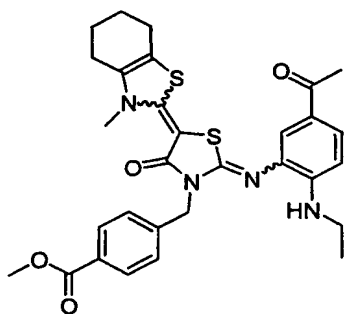
**B. Preparation of methyl 4-[2-(5-acetyl-2-ethylaminophenylimino)-5-(3-methyl-2-(methylthio)benzothiazol-2-ylidene)-4-oxothiazolidin-3-ylmethyl]benzoate**



- 5 The title compound was prepared from intermediate 4-[2-(5-acetyl-2-ethylaminophenylimino)-4-oxothiazolidin-3-ylmethyl]benzoic acid methyl ester and 3-methyl-2-(methylthio)benzothiazol-3-ium *p*-toluenesulfonate in a manner similar to Example 45. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.03 (2H, d), 7.64-7.70 (2H, m), 7.49-7.55 (3H, m), 7.36 (1H, m), 7.20 (1H, m), 7.08 (1H, d), 6.51 (1H, d), 5.24 (2H, s), 4.15 (1H, br t), 3.91 (3H, s), 3.80 (3H, s), 3.04 (2H, m), 2.51 (3H, s), 1.01 (3H, s); MS(ESI): 573 (MH<sup>+</sup>).
- 10

**EXAMPLE 181**

- Preparation of methyl 4-[2-(5-acetyl-2-ethylamino-phenylimino)-5-(3-methyl-4,5,6,7-tetrahydro-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-3-ylmethyl]benzoate**
- 15



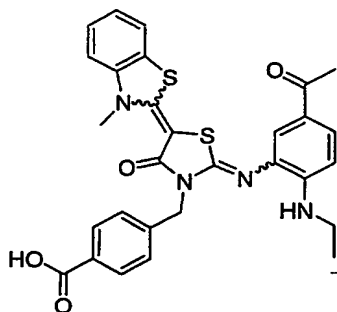
The title compound was prepared in a manner similar to Example 168 by condensing intermediate 3-methyl-2-methylthio-4,5,6,7-tetrahydro-benzothiazol-3-ium *p*-toluenesulfonate with 4-[2-(5-acetyl-2-

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ethylaminophenylimino)-4-oxothiazolidin-3-ylmethyl]benzoic acid methyl ester.  
MS(ESI): 577 (MH<sup>+</sup>).

**EXAMPLE 182**

**Preparation of 4-[2-(5-acetyl-2-ethylaminophenylimino)-5-(3-methyl-3H-  
5 benzothiazol-2-ylidene)-4-oxothiazolidin-3-ylmethyl]benzoic acid**

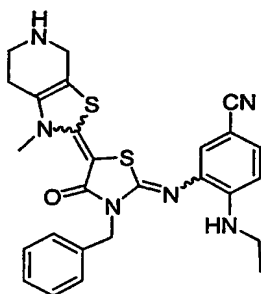


The product of Example 180 was saponified under conditions similar to that described in Example 29 to afford the title compound. MS(ESI): 559 (MH<sup>+</sup>).

10

**EXAMPLE 183**

**Preparation of 3-[3-benzyl-5-(1-methyl-4,5,6,7-tetrahydro-1H-thiazolo[5,4-c]pyridin-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile**



15

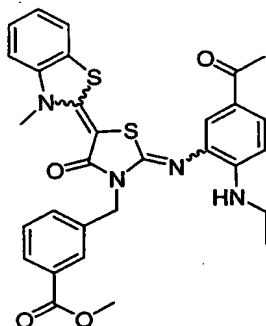
The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 3-bromo-4-oxopiperidine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester—synthesized according to a published procedure [*J. Med. Chem.* 1998, 41, 1409-1416].  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.39-7.43 (2H, m), 7.33 (2H, m), 7.24-7.29 (2H, m), 7.20

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(1H, d), 6.47 (1H, d), 5.15 (2H, s), 4.28 (1H, br t), 3.81 (2H, br s), 3.63 (3H, s), 3.22 (2H, br s), 2.99 (2H, q), 2.49 (2H, br s), 1.01 (3H, t); MS(ESI): 503 (MH<sup>+</sup>).

## EXAMPLE 184

**5 Preparation of methyl 3-[2-(5-acetyl-2-ethylaminophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-3-ylmethyl]benzoate**

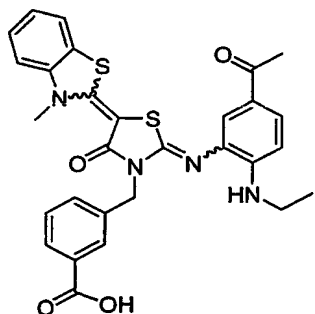


- To a solution of methyl 3-(bromomethyl)benzoate (1.0 g, 4.4 mmol) in anhydrous DMF (10 mL) was added sodium azide (285 mg, 4.4 mmol). The resulting mixture was heated at 50°C for 2h, cooled, diluted with CHCl<sub>3</sub> (100 mL), washed with water (5 x 50 mL), dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to yield methyl 3-(azidomethyl)benzoate (0.84 g, quant.), which was used without purification. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.01 (2H, m), 7.44-7.54 (2H, m), 4.42 (2H, s), 3.94 (3H, s).
- 15** Methyl 3-(azidomethyl)benzoate was transformed into its amine (Staudinger conditions) and then converted into its isocyanate in a manner similar to Example 45. The title compound then was prepared in a manner similar to that described in Example 180 by replacing methyl 4-(isothiocyantomethyl)benzoate with methyl 3-(isothiocyantomethyl)benzoate.
- 20** <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.13 (1H, br s), 7.98 (1H, d), 7.60-7.70 (3H, m), 7.53 (1H, d), 7.43 (1H, m), 7.36 (1H, m), 7.20 (1H, m), 7.07 (1H, d), 6.52 (1H, d), 5.24 (2H, s), 4.20 (1H, br t), 3.90 (3H, s), 3.79 (3H, s), 3.05 (2H, m), 2.51 (3H, s), 1.01 (3H, t); MS(ESI): 573 (MH<sup>+</sup>).

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**EXAMPLE 185**

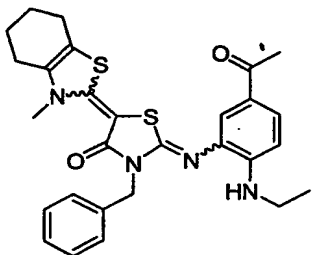
**Preparation of 3-[2-(5-acetyl-2-ethylaminophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-3-ylmethyl]benzoic acid**



- 5        The product of Example 184 was saponified under conditions similar to that described in Example 29 to afford the title compound. MS(ESI): 559 (MH<sup>+</sup>).

**EXAMPLE 186**

- 10        **Preparation of 2-(5-acetyl-2-ethylaminophenylimino)-3-benzyl-5-(3-methyl-4,5,6,7-tetrahydro-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one**

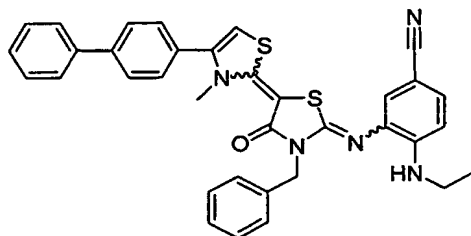


- 15        The title compound was prepared in a manner similar to Example 168 by condensing intermediate 3-methyl-2-methylthio-4,5,6,7-tetrahydro-benzothiazol-3-ium *p*-toluenesulfonate with 2-(5-acetyl-2-ethylaminophenylimino)-3-benzylthiazolidin-4-one. MS(ESI): 519 (MH<sup>+</sup>).

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**EXAMPLE 187**

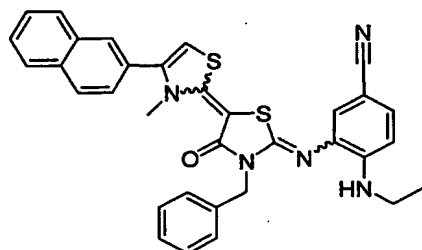
**Preparation of 3-(3'-benzyl-4-biphenyl-4-yl-3-methyl-4'-oxo-3',4'-dihydro-3H-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile**



- 5           The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-4'-phenylacetophenone. MS(ESI): 600 (MH<sup>+</sup>).

**EXAMPLE 188**

- 10           **Preparation of 3-(3'-benzyl-3-methyl-4-naphthalen-2-yl-4'-oxo-3',4'-dihydro-3H-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile**



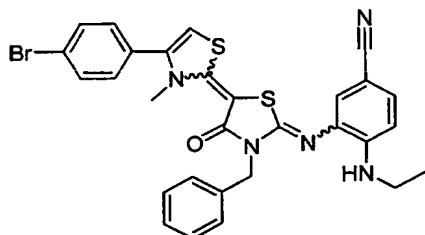
- 15           The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-2'-acetophenone. MS(ESI): 574 (MH<sup>+</sup>).



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**EXAMPLE 189**

**Preparation of 3-[3'-b nzyI-4-(4-bromophenyl)-3-methyl-4'-oxo-3',4'-dihydro-3H-[2,5]bithiazolyIiden-2'-ylideneamino]-4-ethylaminobenzonitrile**

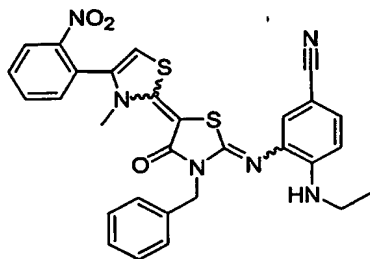


5

The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2,4'-dibromoacetophenone. MS(ESI): 602 (MH<sup>+</sup>).

**EXAMPLE 190**

**10 Preparation of 3-[3'-benzyl-3-methyl-4-(2-nitrophenyl)-4'-oxo-3',4'-dihydro-3H-[2,5]bithiazolyIiden-2'-ylideneamino]-4-ethylaminobenzonitrile**

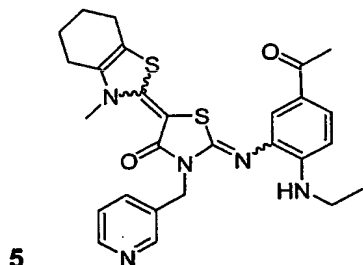


**15** The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-2'-nitroacetophenone. MS(ESI): 569 (MH<sup>+</sup>).

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## EXAMPLE 191

**Preparation of 2-(5-acetyl-2-ethylaminophenylimino)-5-(3-methyl-4,5,6,7-tetrahydro-3*H*-benzothiazol-2-ylidene)-3-pyridin-3-ylmethylthiazolidin-4-one**

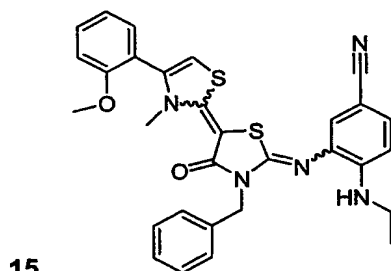


The title compound was prepared in a manner similar to Example 168 by condensing intermediate 3-methyl-2-methylthio-4,5,6,7-tetrahydro-benzothiazol-3-ium *p*-toluenesulfonate with 2-(5-acetyl-2-ethylaminophenylimino)-3-pyridin-3-ylmethyl-thiazolidin-4-one. MS(ESI): 520 (MH<sup>+</sup>).

10

## EXAMPLE 192

**Preparation of 3-[3'-benzyl-4-(2-methoxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5]bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile**

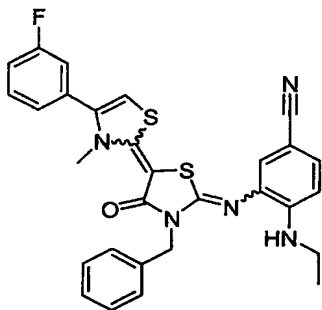


The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-2'-methoxyacetophenone. MS(ESI): 554 (MH<sup>+</sup>).

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**EXAMPLE 193**

**Preparation of 3-[3'-benzyl-4-(3-fluorophenyl)-3-methyl-4'-oxo-3',4'-dihydro-3H-[2,5]bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile**

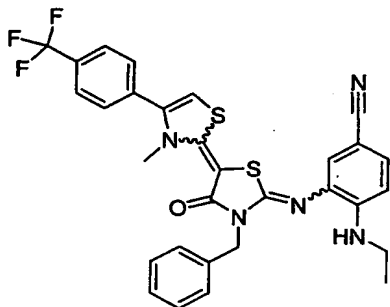


5

The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-3'-fluoroacetophenone. MS(ESI): 542 (MH<sup>+</sup>).

**EXAMPLE 194**

**10 Preparation of 3-[3'-benzyl-3-methyl-4'-oxo-4-(4-trifluoromethylphenyl)-3',4'-dihydro-3H-[2,5]bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile**

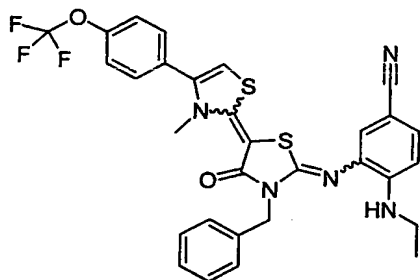


**15** The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-4'-trifluoromethyl-acetophenone. MS(ESI): 592 (MH<sup>+</sup>).

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## EXAMPLE 195

Preparation of 3-[3'-benzyl-3-methyl-4'-oxo-4-(4-trifluoromethoxyphenyl)-3',4'-dihydro-3H-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile

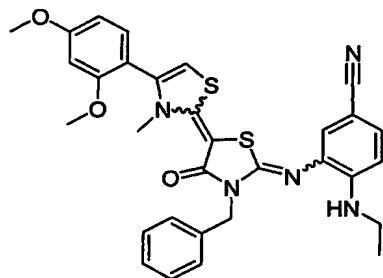


5

The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-4'-(trifluoromethoxy)acetophenone. MS(ESI): 608 (MH<sup>+</sup>).

## EXAMPLE 196

10 Preparation of 3-[3'-benzyl-4-(2,4-dimethoxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3H-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile

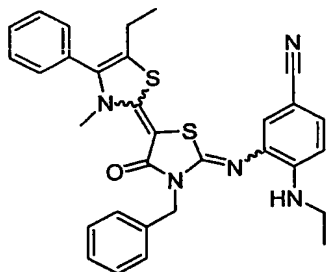


15 The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-2',4'-dimethoxyacetophenone. MS(ESI): 584 (MH<sup>+</sup>).

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**EXAMPLE 197**

**Preparation of 3-(3'-benzyl-5-ethyl-3-methyl-4'-oxo-4-phenyl-3',4'-dihydro-3H-[2,5]bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile**

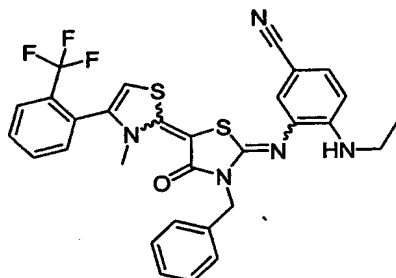


5

The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromobutyrophenone. MS(ESI): 552 (MH<sup>+</sup>).

**EXAMPLE 198**

**10 Preparation of 3-[3'-benzyl-3-methyl-4'-oxo-4-(2-trifluoromethylphenyl)-3',4'-dihydro-3H-[2,5]bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile**

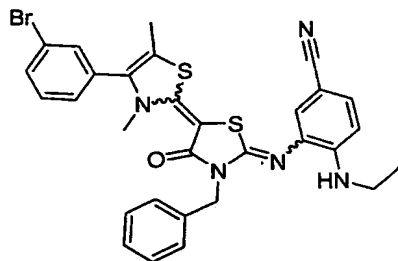


**15** The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-2'-(trifluoromethyl)acetophenone. MS(ESI): 592 (MH<sup>+</sup>).

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**EXAMPLE 199**

**Preparation of 3-[3'-benzyl-4-(3-bromophenyl)-3,5-dimethyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile**

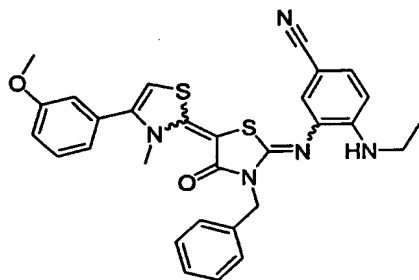


5

The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2,3'-dibromopropiophenone. MS(ESI): 617 (MH<sup>+</sup>).

**EXAMPLE 200**

**10 Preparation of 3-[3'-benzyl-4-(3-methoxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile**

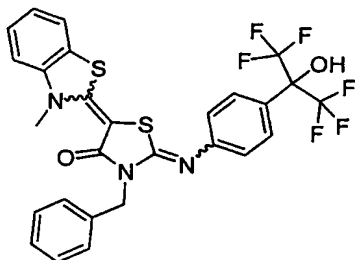


**15** The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 2-bromo-3'-methoxyacetophenone. MS(ESI): 554 (MH<sup>+</sup>).

**EXAMPLE 201**

**Preparation of 3-benzyl-2-[4-(1,1,1,3,3,3-hexafluoro-2-hydroxyisopropyl)-phenylimino]-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one**

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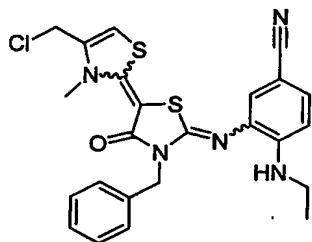


The title compound was prepared in a manner similar to that described in Example 52 by replacing aniline with 4-(1,1,1,3,3,3-hexafluoro-2-hydroxyisopropyl)aniline. MS(ESI): 596 (MH<sup>+</sup>).

5

**EXAMPLE 202**

**Preparation of 3-(3'-benzyl-4-chloromethyl-3-methyl-4'-oxo-3',4'-dihydro-3H-[2,5]bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile**



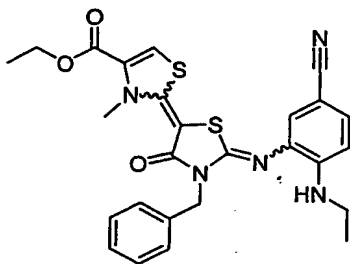
The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 1,3-dichloroacetone. MS(ESI): 496 (MH<sup>+</sup>).

10

**EXAMPLE 203**

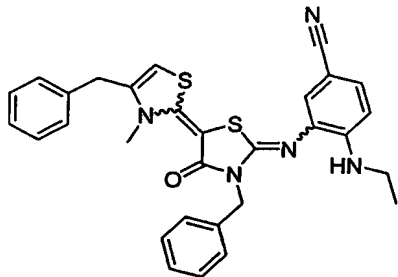
**Preparation of 3'-benzyl-2'-(5-cyano-2-ethylaminophenylimino)-3-methyl-4'-oxo-3',4'-dihydro-3H,2'H-[2,5]bithiazolylidene-4-carboxylic acid ethyl**

15 ester

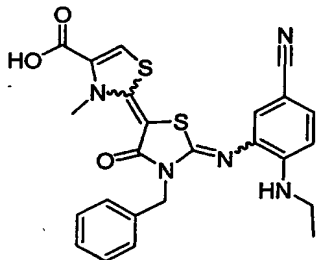


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The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with ethyl bromopyruvate. MS(ESI): 520 (MH<sup>+</sup>).

**EXAMPLE 204****5 Preparation of 3-(4,3'-dibenzyl-3-methyl-4'-oxo-3',4'-dihydro-3H-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile**

The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 1-chloro-3-phenylpropan-2-one. MS(ESI): 538 (MH<sup>+</sup>).

**EXAMPLE 205****10 Preparation of 3'-benzyl-2'-(5-cyano-2-ethylaminophenylimino)-3-methyl-4'-oxo-3',4'-dihydro-3H,2'H-[2,5']bithiazolylidene-4-carboxylic acid**

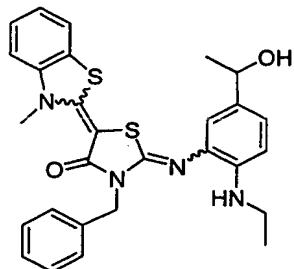
**15** The product of Example 203 was saponified under conditions similar to that described in Example 29 to afford the title compound. MS(ESI): 492 (MH<sup>+</sup>).



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**EXAMPLE 206**

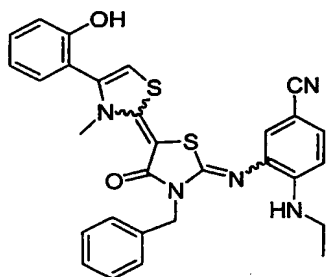
**Preparation of 3-benzyl-2-[2-ethylamino-5-(1-hydroxyethyl)phenylimino]-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one**



- 5 The product of Example 38 was reduced with sodium borohydride in 1:1 MeOH/THF and chromatographed (TEA-washed silica gel, 0-10% MeOH/DCM) to afford the title compound. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.47-7.54 (3H, m), 7.28-7.37 (4H, m), 7.17 (1H, m), 6.99-7.06 (3H, m), 6.57 (1H, d), 5.19 (2H, s), 4.80 (1H, q), 3.76 (3H, s), 3.01 (2H, q), 1.48 (3H, d), 1.04 (3H, s); MS(ESI):
- 10 517 (MH<sup>+</sup>).

**EXAMPLE 207**

**Preparation of 3-[3'-benzyl-4-(2-hydroxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile**



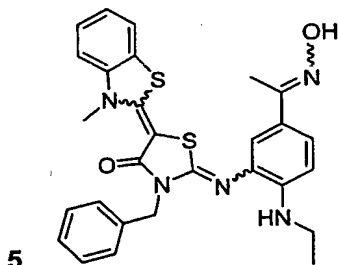
15

The product of Example 192 was treated with boron tribromide in DCM at 25°C. After 15 min the product mixture was quenched with brine, concentrated and chromatographed (silica gel, 0-10% MeOH/DCM) to yield the title compound. MS(ESI): 540 (MH<sup>+</sup>).

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## EXAMPLE 208

Preparation of 3-benzyl-2-[2-ethylamino-5-(1-hydroxyiminoethyl)phenylimino]-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one



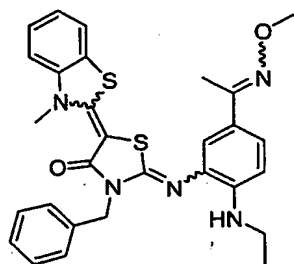
To the product of Example 38 was added hydroxylamine hydrochloride (2 equiv) and pyridine. The resulting mixture was heated at 80°C for 24h, cooled, concentrated and chromatographed (TEA-washed silica gel, 0-50% EtOAc/Hex) to give the title compound. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ 11.07 (1H, s), 7.88 (1H, s), 7.67 (2H, m), 7.53 (1H, d), 7.39 (2H, m), 7.21-7.33 (5H, m), 7.09-7.14 (1H, m), 5.05 (2H, s), 3.92 (2H, q), 3.27 (3H, s), 2.23 (3H, s), 1.03 (3H, t); MS(ESI): 530 (MH<sup>+</sup>).

10

## EXAMPLE 209

Preparation of 3-benzyl-2-[2-ethylamino-5-(1-methoxyiminoethyl)phenylimino]-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one

15

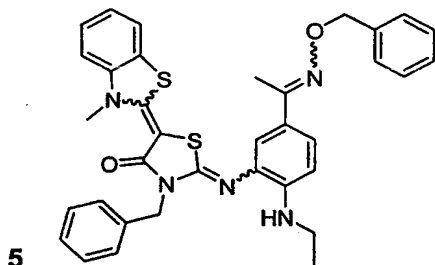


The title compound was prepared in a manner similar to that described in Example 208 by replacing hydroxylamine hydrochloride with O-methylhydroxylamine hydrochloride. MS(ESI): 544 (MH<sup>+</sup>).

20

## EXAMPLE 210

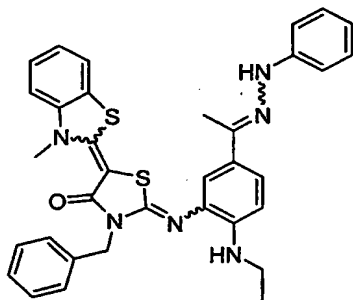
Preparation of 3-benzyl-2-[5-(1-benzyloxyiminoethyl)-2-ethylaminophenylimino]-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one



The title compound was prepared in a manner similar to that described in Example 208 by replacing hydroxylamine hydrochloride with *O*-benzylhydroxylamine hydrochloride. MS(ESI): 620 (MH<sup>+</sup>).

## EXAMPLE 211

10 Preparation of 3-benzyl-2-[2-ethylamino-5-[1-(phenylhydrazono)ethyl]-phenylimino]-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one



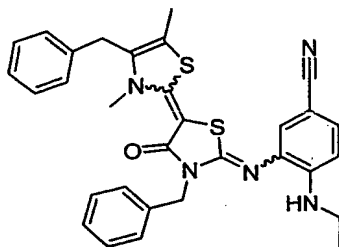
The title compound was prepared in a manner similar to that described in Example 208 by replacing hydroxylamine hydrochloride with phenylhydrazine. MS(ESI): 605 (MH<sup>+</sup>).

15

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## EXAMPLE 212

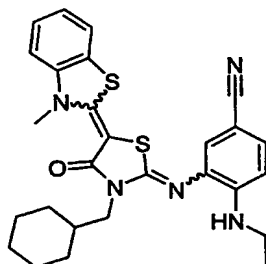
Preparation of 3-(4,3'-dibenzyl-3,5-dimethyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile



- 5 The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 3-chloro-1-phenylbutan-2-one. MS(ESI): 552 (MH<sup>+</sup>).

## EXAMPLE 213

- 10 Preparation of 3-[3-cyclohexylmethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile

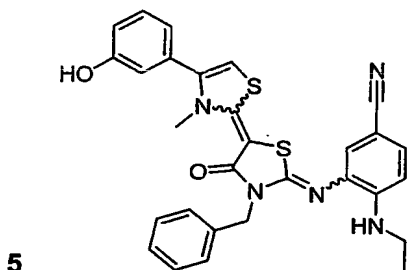


The title compound was prepared in a manner similar to that described in Example 83 by replacing 3-picolyl isothiocyanate hydrobromide with cyclohexylmethyl isothiocyanate. MS(ESI): 504 (MH<sup>+</sup>).

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**EXAMPLE 214**

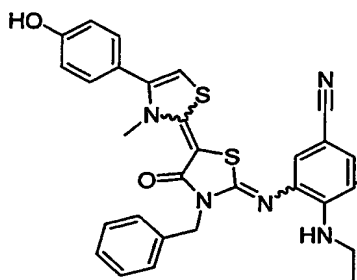
**Preparation of 3-[3'-benzyl-4-(3-hydroxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3H-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile**



The title compound was prepared from the product of Example 200 in a manner similar to that described in Example 207. MS(ESI): 540 (MH<sup>+</sup>).

**EXAMPLE 215**

10 **Preparation of 3-[3'-benzyl-4-(4-hydroxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3H-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile**

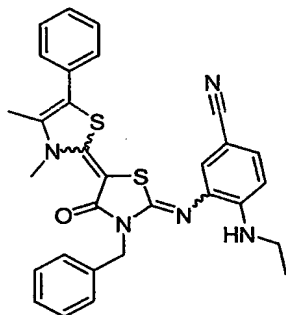


The title compound was prepared from the product of Example 174 in a manner similar to that described in Example 207. MS(ESI): 540 (MH<sup>+</sup>).

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**EXAMPLE 216**

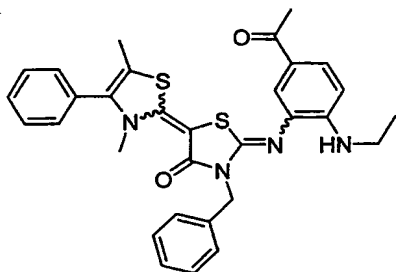
**Preparation of 3-(3'-benzyl-3,4-dimethyl-4'-oxo-5-phenyl-3',4'-dihydro-3H-[2,5]bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile**



- 5 The title compound was prepared in a manner similar to that described in Example 52 by replacing 2-bromopropiophenone with 1-chloro-1-phenylpropan-2-one—generated in situ by addition of methylmagnesium chloride to chlorophenylacetyl chloride (-78 to 25°C). MS(ESI): 538 (MH<sup>+</sup>).

**EXAMPLE 217**

- 10 **Preparation of 2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-3,5-dimethyl-4-phenyl-2',3'-dihydro-3H-[2,5]bithiazolyliden-4'-one**



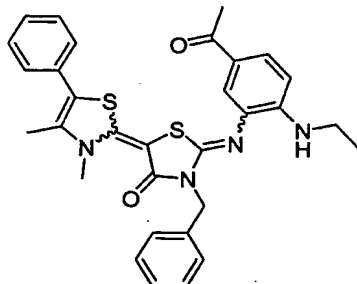
T

- he title compound was prepared in a manner similar to that described in Example 52 by replacing 3-amino-4-ethylaminobenzonitrile with 3'-amino-4'-ethylaminoacetophenone. MS(ESI): 555 (MH<sup>+</sup>).

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**EXAMPLE 218**

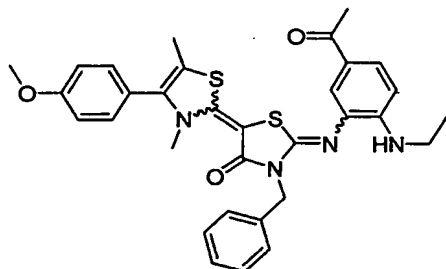
**Preparation of 2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-3,4-dimethyl-5-phenyl-2',3'-dihydro-3H-[2,5']bithiazolyliden-4'-one**



- 5 The title compound was prepared in a manner similar to that described in Example 217 by replacing 2-bromopropiophenone with 1-chloro-1-phenylpropan-2-one. MS(ESI): 555 (MH<sup>+</sup>).

**EXAMPLE 219**

- 10 **Preparation of 2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-4-(4-methoxyphenyl)-3,5-dimethyl-2',3'-dihydro-3H-[2,5']bithiazolyliden-4'-one**

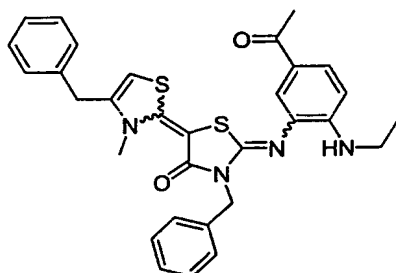


The title compound was prepared in a manner similar to that described in Example 217 by replacing 2-bromopropiophenone with 2-bromo-4'-methoxypropiophenone. MS(ESI): 585 (MH<sup>+</sup>).

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## EXAMPLE 220

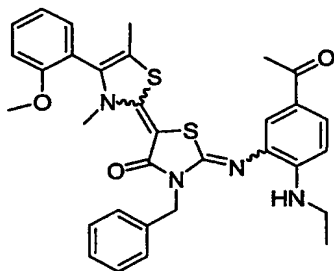
Preparation of 2'-(5-acetyl-2-ethylaminophenylimino)-4,3'-dibenzyl-3-methyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one



- 5 The title compound was prepared in a manner similar to that described in Example 217 by replacing 2-bromopropiophenone with 1-chloro-3-phenylpropan-2-one. MS(ESI): 555 (MH<sup>+</sup>).

## EXAMPLE 221

- 10 Preparation of 2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-4-(2-methoxyphenyl)-3,5-dimethyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one



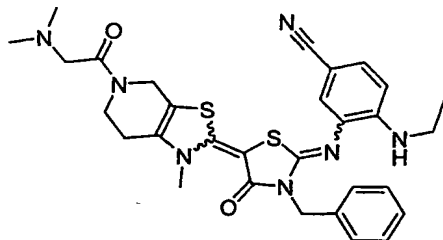
The title compound was prepared in a manner similar to that described in Example 217 by replacing 2-bromopropiophenone with 2-bromo-2'-methoxypropiophenone. MS(ESI): 585 (MH<sup>+</sup>).



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## EXAMPLE 222

Preparation of 3-{3-benzyl-5-[5-(2-dimethylaminoacetyl)-1-methyl-4,5,6,7-tetrahydro-1*H*-thiazolo[5,4-*c*]pyridin-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile



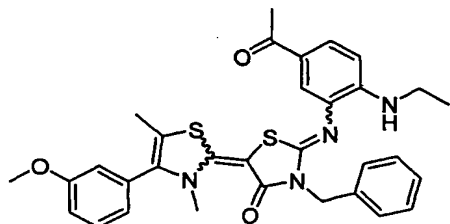
5

To the product of Example 183 in  $\text{CHCl}_3$  was added *N,N*-dimethylaminoacetyl chloride and TEA. After 4h the product mixture was concentrated and chromatographed (silica gel, 0-40% EtOAc/Hex) to yield the title compound.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.39-7.44 (2H, m), 7.33 (2H, m), 7.23-7.30 (2H m), 7.19 (1H, br s), 6.47 (1H, d), 5.15 (2H, s), 4.61 (1H, br s), 4.51 (1H, br s), 4.27 (1H, m), 3.92 (2H, m), 3.64 (3H, br s), 3.22 (1H, br s), 3.16 (1H, br s), 2.99 (2H, m), 2.63 (1H, br s), 2.56 (1H, br s), 2.31 (3H, s), 2.28 (3H, s), 1.01 (3H, t); MS(ESI): 588 ( $\text{MH}^+$ ).

10

## EXAMPLE 223

15 Preparation of 2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-4-(3-methoxyphenyl)-3,5-dimethyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one



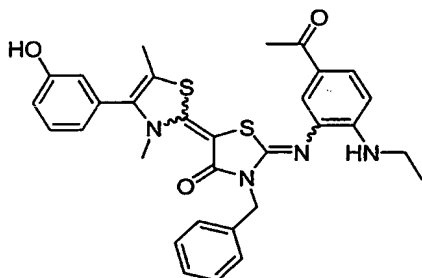
The title compound was prepared in a manner similar to that described in Example 217 by replacing 2-bromopropiophenone with 2-bromo-3'-methoxypropiophenone. MS(ESI): 585 ( $\text{MH}^+$ ).

20

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**EXAMPLE 224**

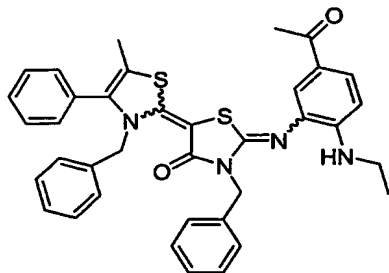
**Preparation of 2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-4-(3-hydroxyphenyl)-3,5-dimethyl-2',3'-dihydro-3H-[2,5]bithiazolyliden-4'-one**



- 5 The title compound was prepared from the product of Example 223 in a manner similar to that described in Example 207. MS(ESI): 571 (MH<sup>+</sup>).

**EXAMPLE 225**

**Preparation of 2'-(5-acetyl-2-ethylaminophenylimino)-3,3'-dibenzyl-5-methyl-4-phenyl-2',3'-dihydro-3H-[2,5]bithiazolyliden-4'-one**



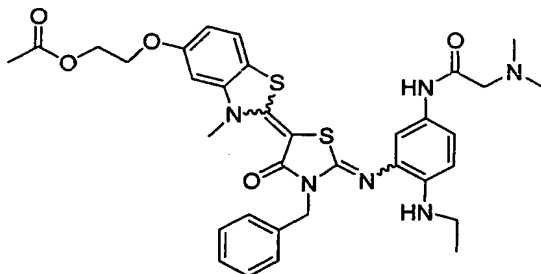
10

- The title compound was prepared in a manner similar to that described in Example 52 by replacing triethylammonium methyldithiocarbamate with triethylammonium benzyldithiocarbamate—generated from benzylamine, carbon disulfide and TEA. MS(ESI): 631 (MH<sup>+</sup>).

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## EXAMPLE 226

Preparation of N-(3-{3-benzyl-5-[5-(2-acetoxyethoxy)-3-methyl-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminophenyl)-2-dimethylamino-acetamide



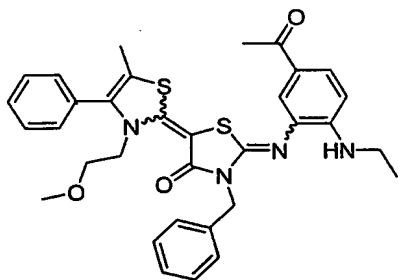
5

- To the product of Example 145 (21 mg, 32  $\mu$ mol) in acetone (2 mL) was added tetra-*n*-butylammonium iodide (24 mg, 65  $\mu$ mol). The solution was stirred at 40°C for 17h prior to the addition of sodium acetate (50 mg, 0.64 mmol). The reaction solution was heated at 75°C for 48h. After cooling the solution was diluted with EtOAc (25 mL), washed with satd NaHCO<sub>3</sub> (20 mL) and water (2 x 20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The crude sample was chromatographed (silica gel, DCM ) to provide the title compound (7 mg, 33%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  7.87 (1H, s), 7.60 (1H, dd), 7.30-7.35 (3H, m), 7.17-7.22 (3H, m), 6.60 (1H, dd), 6.48 (1H, d), 5.27 (2H, s), 4.72 (1H, s), 4.39 (2H, t), 4.16 (2H, t), 3.69 (2H, q), 3.16 (2H, s), 3.08 (3H, s), 2.43 (6H, s), 2.06 (3H, s), 0.91 (3H, t); MS(ESI): 675 (MH<sup>+</sup>).
- 10
- 15

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## EXAMPLE 227

Preparation of 2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-3-(2-methoxyethyl)-5-methyl-4-phenyl-2',3'-dihydro-3H-[2,5']bithiazolyliden-4'-one



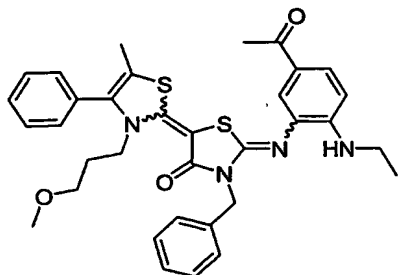
5

The title compound was prepared in a manner similar to that described in Example 52 by replacing triethylammonium methyldithiocarbamate with triethylammonium 2-methoxyethyldithiocarbamate—generated from 2-methoxy-ethylamine, carbon disulfide and TEA. MS(ESI): 599 (MH<sup>+</sup>).

10

## EXAMPLE 228

Preparation of 2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-3-(3-methoxypropyl)-5-methyl-4-phenyl-2',3'-dihydro-3H-[2,5']bithiazolyliden-4'-one



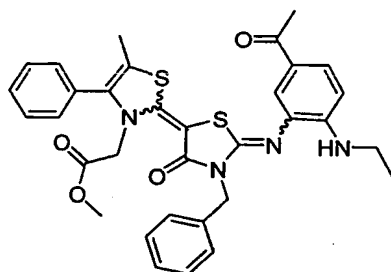
15

The title compound was prepared in a manner similar to that described in Example 52 by replacing triethylammonium methyldithiocarbamate with triethylammonium 3-methoxypropyldithiocarbamate—generated from 2-methoxy-propylamine, carbon disulfide and TEA. MS(ESI): 613 (MH<sup>+</sup>).

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**EXAMPLE 229**

**Preparation of [2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-5-methyl-4'-oxo-4-phenyl-3',4'-dihydro-2'H-[2,5']bithiazolyliden-3-yl]acetic acid methyl ester**



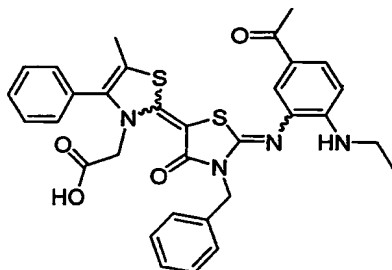
5

The title compound was prepared in a manner similar to that described in Example 52 by replacing triethylammonium methyldithiocarbamate with triethylammonium methoxycarbonylmethyldithiocarbamate—generated from glycine methyl ester, carbon disulfide and TEA. MS(ESI): 613 (MH<sup>+</sup>).

10

**EXAMPLE 230**

**Preparation of [2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-5-methyl-4'-oxo-4-phenyl-3',4'-dihydro-2'H-[2,5']bithiazolyliden-3-yl]acetic acid**

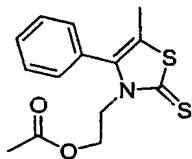


15

The product of Example 229 was saponified under conditions similar to that described in Example 29 to afford the title compound. MS(ESI): 599 (MH<sup>+</sup>).

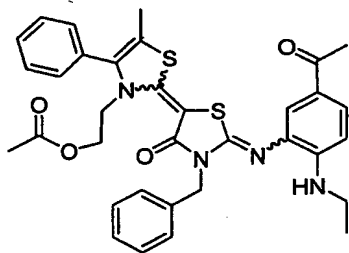
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## EXAMPLE 231

**A. Preparation of 2-(5-methyl-4-phenyl-2-thioxothiazol-3-yl)ethyl acetate**

5            3-(2-Hydroxyethyl)-5-methyl-4-phenyl-3*H*-thiazole-2-thione was prepared in a manner similar to that described in Example 52 by replacing triethylammonium methyldithiocarbamate with triethylammonium 2-hydroxyethylthiocarbamate—generated from ethanolamine, carbon disulfide and TEA.

10           Intermediate 3-(2-hydroxyethyl)-5-methyl-4-phenyl-3*H*-thiazole-2-thione was treated with acetic anhydride (1 equiv) and TEA (2 equiv) in CHCl<sub>3</sub>. After 12h the product mixture was concentrated and chromatographed (silica gel, 0-40% EtOAc/Hex) to afford the title compound. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.50-7.55 (3H, m), 7.28-7.32 (2H, m), 4.32 (2H, t), 4.26 (2H, t), 2.03 (3H, s), 1.93 (3H, s).

**B. Preparation of 2-[2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-5-methyl-4'-oxo-4-phenyl-3',4'-dihydro-2'*H*-[2,5']bithiazolyliden-3-yl]ethyl acetate**

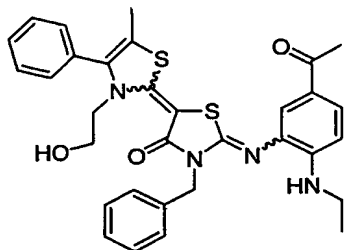
20           In a manner similar to that described in Example 52, intermediate 2-(5-methyl-4-phenyl-2-thioxothiazol-3-yl)ethyl acetate was alkylated with methyl *p*-toluenesulfonate and condensed with 2-(5-acetyl-2-ethylaminophenylimino)-3-benzylthiazolidin-4-one to yield the title compound. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.63-7.67 (2H, m), 7.44-7.51 (5H, m), 7.28-7.37 (5H, m), 6.50 (1H, d), 5.19 (2H, s),

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4.30 (1H, br t), 4.03 (4H, m), 3.06 (2H, m), 2.48 (3H, s), 2.05 (3H, s), 1.89 (3H, s), 1.05 (3H, t); MS(ESI): 627 (MH<sup>+</sup>).

**EXAMPLE 232**

**Preparation of 2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-3-(2-hydroxyethyl)-5-methyl-4-phenyl-2',3'-dihydro-3H-[2,5']bithiazolyliden-4'-one**

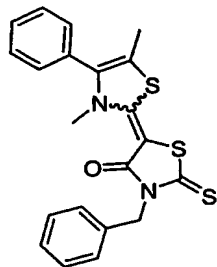


The product of Example 231 was saponified under conditions similar to that described in Example 29 to afford the title compound. MS(ESI): 585

(MH<sup>+</sup>).

**EXAMPLE 233**

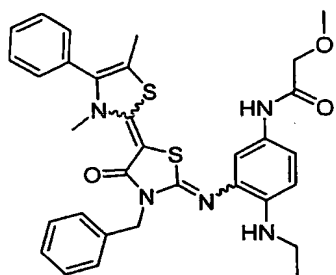
**A. Preparation of 3'-benzyl-3,5-dimethyl-4-phenyl-2'-thioxo-2',3'-dihydro-3H-[2,5']bithiazolyliden-4'-one**



The title compound was prepared in a manner similar to that described in Example 1 by replacing 2-methylthiobenzothiazole with 3,5-dimethyl-4-phenyl-3H-thiazole-2-thione. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.50-7.58 (5H, m), 7.23-7.32 (5H, m), 5.39 (2H, s), 3.54 (3H, s), 2.11 (3H, s).

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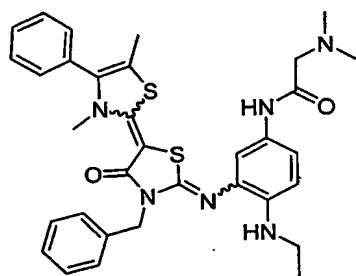
**B. Preparation of N-[3-(3'-benzyl-3,5-dimethyl-4'-oxo-4-phenyl-3',4'-dihydro-3H-[2,5]bithiazolyliden-2'-ylideneamino)-4-ethylaminophenyl]-2-methoxyacetamide**



- 5 Likewise as described in Example 1, intermediate 3'-benzyl-3,5-dimethyl-4-phenyl-2'-thioxo-2',3'-dihydro-3H-[2,5]bithiazolyliden-4'-one was alkylated with methyl *p*-toluenesulfonate and condensed with *N*-(3-amino-4-ethylaminophenyl)-2-methoxyacetamide to afford the title compound. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.00 (1H, br s), 7.42-7.51 (5H, m), 7.30-7.37 (3H, m), 7.19-7.26 (3H, m), 7.11 (1H, d), 6.53 (1H, br s), 5.18 (2H, s), 3.97 (2H, s), 3.47 (3H, s), 3.42 (3H, s), 2.98 (2H, m), 2.06 (3H, s), 1.02 (3H, br t); MS(ESI): 600 (MH<sup>+</sup>).
- 10

**EXAMPLE 234**

- Preparation of N-[3-(3'-benzyl-3,5-dimethyl-4'-oxo-4-phenyl-3',4'-dihydro-3H-[2,5]bithiazolyliden-2'-ylideneamino)-4-ethylaminophenyl]-2-dimethylaminoacetamide**
- 15



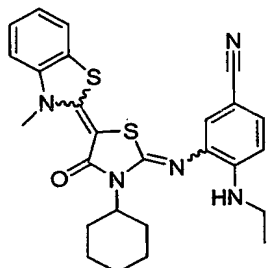
- The title compound was prepared in a manner similar to that described in Example 233 by replacing *N*-(3-amino-4-ethylaminophenyl)-2-methoxyacetamide with *N*-(3-amino-4-ethylaminophenyl)-2-dimethylaminoacetamide. MS(ESI): 613 (MH<sup>+</sup>).
- 20



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## EXAMPLE 235

Preparation of 3-[3-cyclohexyl-5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile



5

To a biphasic mixture of cyclohexylamine (2.3 mL, 20 mmol) in  $\text{CHCl}_3$  (60 mL) and satd aqueous  $\text{NaHCO}_3$  (40 mL) was added a solution of  $\text{CSCl}_2$  (1.57 mL, 20 mmol) in  $\text{CHCl}_3$  (5 mL) dropwise at  $5^\circ\text{C}$ . The mixture was stirred 1h at  $5^\circ\text{C}$ . Methyl thioglycolate (1.9 mL, 20 mmol) was added, and the mixture  
10 was stirred overnight at  $20^\circ\text{C}$ . The organic layer was separated, and the aqueous layer was extracted with  $\text{CHCl}_3$ . The combined organic layers were washed with water, 1N HCl, water, satd aqueous  $\text{NaHCO}_3$  and then dried over  $\text{MgSO}_4$ . Evaporation of solvent under reduced pressure gave a crude material, which was used in the next step without purification.

15 To a solution of the above product in toluene (80 mL) was added TsOH (100 mg), and the mixture was heated at reflux for 8h with a dropping funnel containing 4Å molecular sieves attached to the flask. After cooling, solid was removed by filtration. Evaporation of the filtrate gave a crude, which was purified by column chromatography on silica gel, eluting with EtOAc-Hex  
20 (0:100 to 3:7) to afford 3-cyclohexylrhodanine (1.24 g).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  4.86 (1H, m), 3.82 (2H, s), 2.30 (2H, q), 1.86 (2H, m), 1.58-1.72 (3H, m), 1.16-1.42 (3H, m).

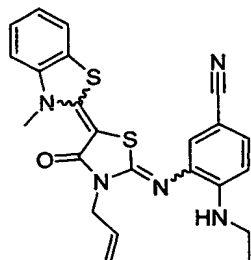
The title compound was prepared in a manner similar to that described in Example 32 by replacing 3-benzylrhodanine with 3-cyclohexylrhodanine.

25 MS(ESI): 490 ( $\text{MH}^+$ ).

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**EXAMPLE 236**

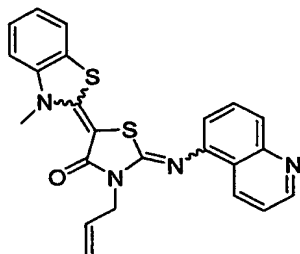
**Preparation of 3-[3-allyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile**



- 5 The title compound was prepared in a manner similar to that described in Example 235 by replacing cyclohexylamine with allylamine. MS(ESI): 448 (MH<sup>+</sup>).

**EXAMPLE 237**

- 10 **Preparation of 3-allyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(quinolin-5-ylimino)thiazolidin-4-one**

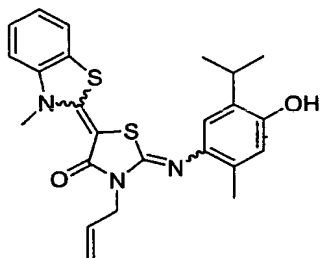


The title compound was prepared in a manner similar to that described in Example 236 by replacing 3-amino-4-ethylaminobenzonitrile with 5-aminoquinoline. MS(ESI): 431 (MH<sup>+</sup>).

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**EXAMPLE 238**

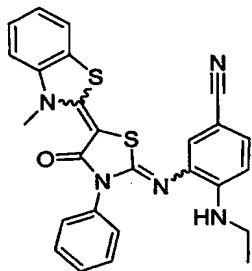
**Preparation of 3-allyl-2-(4-hydroxy-5-isopropyl-2-methylphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one**



- 5        The title compound was prepared in a manner similar to that described in Example 236 by replacing 3-amino-4-ethylaminobenzonitrile with 4-aminothymol hydrochloride. MS(ESI): 452 (MH<sup>+</sup>).

**EXAMPLE 239**

- 10      **Preparation of 4-ethylamino-3-[5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-3-phenylthiazolidin-2-ylideneamino]benzonitrile**

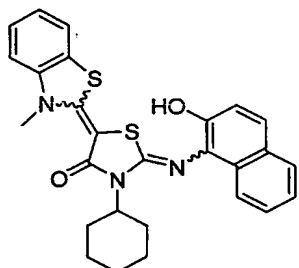


The title compound was prepared in a manner similar to that described in Example 235 by replacing cyclohexylamine with aniline. MS(ESI): 484 (MH<sup>+</sup>).

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**EXAMPLE 240**

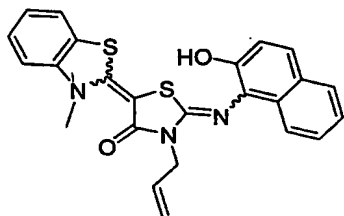
**Preparation of 3-cyclohexyl-2-(2-hydroxynaphthalen-1-ylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one**



- 5 The title compound was prepared in a manner similar to that described in Example 235 by replacing 3-amino-4-ethylaminobenzonitrile with 1-amino-2-naphthol hydrochloride. MS(ESI): 488 (MH<sup>+</sup>).

**EXAMPLE 241**

- 10 **Preparation of 3-allyl-2-(2-hydroxynaphthalen-1-ylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one**

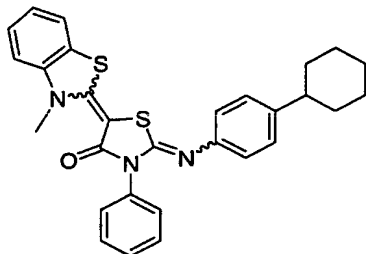


The title compound was prepared in a manner similar to that described in Example 236 by replacing 3-amino-4-ethylaminobenzonitrile with 1-amino-2-naphthol hydrochloride. MS(ESI): 446 (MH<sup>+</sup>).

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**EXAMPLE 242**

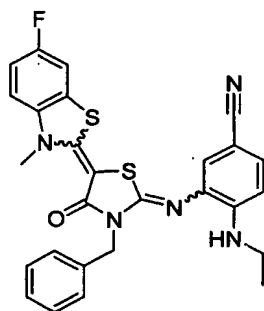
**Preparation of 2-(4-cyclohexylphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-3-phenylthiazolidin-4-one**



- 5 The title compound was prepared in a manner similar to that described in Example 239 by replacing 3-amino-4-ethylaminobenzonitrile with 4-cyclohexylaniline. MS(ESI): 498 (MH<sup>+</sup>).

**EXAMPLE 243**

- 10 **Preparation of 3-[3-benzyl-5-(6-fluoro-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile**

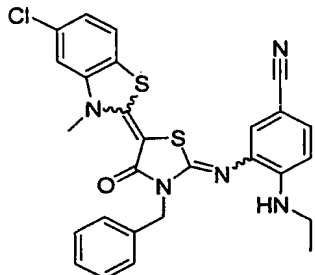


The title compound was prepared in a manner similar to that described in Example 55 by replacing 2-mercapto-5-trifluoromethylbenzothiazole with 6-fluoro-2-mercaptobenzothiazole. MS(ESI): 516 (MH<sup>+</sup>).

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**EXAMPLE 244**

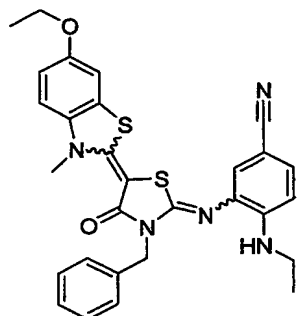
**Preparation of 3-[3-benzyl-5-(5-chloro-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile**



- 5 The title compound was prepared in a manner similar to that described in Example 55 by replacing 2-mercapto-5-trifluoromethylbenzothiazole with 5-chloro-2-mercaptobenzothiazole. MS(ESI): 532 (MH<sup>+</sup>).

**EXAMPLE 245**

- 10 **Preparation of 3-[3-benzyl-5-(6-ethoxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile**

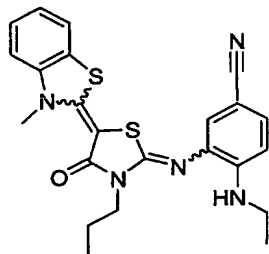


The title compound was prepared in a manner similar to that described in Example 55 by replacing 2-mercapto-5-trifluoromethylbenzothiazole with 6-ethoxy-2-mercaptobenzothiazole. MS(ESI): 542 (MH<sup>+</sup>).

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## EXAMPLE 246

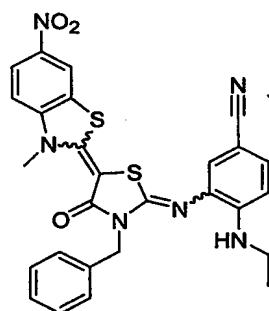
Preparation of 4-ethylamino-3-[5-(3-methyl-3H-benzothiazol-2-ylidene)-4-oxo-3-propylthiazolidin-2-ylideneamino]benzonitrile



- 5 The title compound was prepared in a manner similar to that described in Example 235 by replacing cyclohexylamine with propylamine. MS(ESI): 450 (MH<sup>+</sup>).

## EXAMPLE 247

- 10 Preparation of 3-[3-benzyl-5-(3-methyl-6-nitro-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile

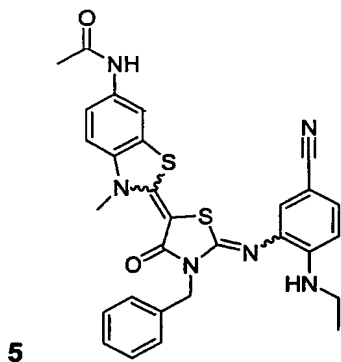


The title compound was prepared in a manner similar to that described in Example 55 by replacing 2-mercapto-5-trifluoromethylbenzothiazole with 2-mercapto-6-nitrobenzothiazole. MS(ESI): 543 (MH<sup>+</sup>).

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## EXAMPLE 248

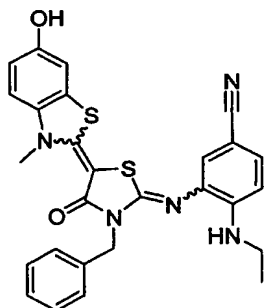
Preparation of N-[2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl]acetamide



The title compound was prepared in a manner similar to that described in Example 55 by replacing 2-mercapto-5-trifluoromethylbenzothiazole with 2-mercapto-6-acetamidobenzothiazole. MS(ESI): 555 (MH<sup>+</sup>).

## EXAMPLE 249

10 Preparation of 3-[3-benzyl-5-(6-hydroxy-3-methyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile



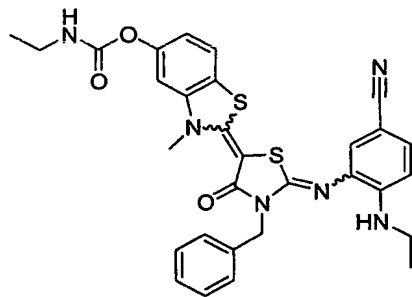
The title compound was prepared from the product of Example 245 in a manner similar to that described in Example 57. MS(ESI): 514 (MH<sup>+</sup>).



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## EXAMPLE 250

**Preparation of ethylcarbamic acid 2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yl ester**

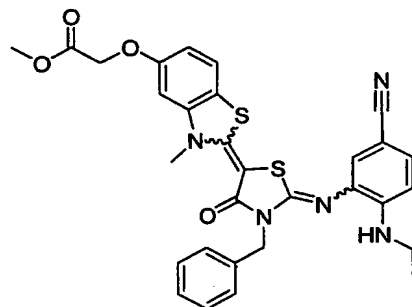


5

The title compound was prepared in a manner similar to that described in Example 58 by replacing dimethylcarbamoil chloride with ethyl isocyanate. MS(ESI): 585 (MH<sup>+</sup>).

## EXAMPLE 251

**10 Preparation of {2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yloxy}acetic acid methyl ester**



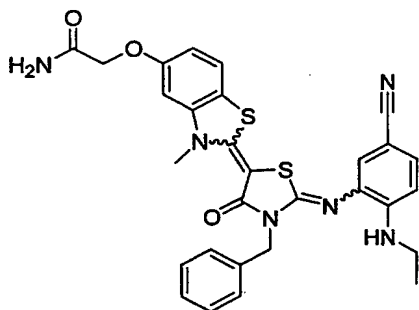
**15** To a suspension of K<sub>2</sub>CO<sub>3</sub> (41 mg, 5 equiv) in 2-butanone (2 mL) were added the product of Example 57 (31 mg, 0.06 mmol) and methyl 2-bromoacetate (7 μL, 1.2 equiv). The resulting suspension was heated at 75°C overnight. After cooling, the reaction mixture was filtered, and the filtrate was evaporated to give a crude material, which was purified by chromatography on silica gel, eluting with MeOH-DCM (0:100 to 3:97) to give the title

compound (5 mg). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.63 (1H, d), 7.28-7.39 (6H, m), 7.13 (1H, d), 7.08 (1H, d), 6.84 (1H, dd), 6.62 (1H, d), 5.13 (2H, s), 4.98 (1H, t), 4.88 (2H, s), 3.79 (3H, s), 3.68 (3H, s), 3.05 (2H, m), 0.99 (3H, t); MS(ESI): 586 (MH<sup>+</sup>).

**5**

### EXAMPLE 252

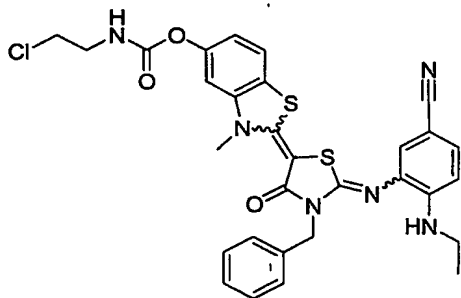
**Preparation of 2-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yloxy}acetamide**



**10** The title compound was prepared in a manner similar to that described in Example 251 by replacing methyl 2-bromoacetate with 2-bromoacetamide. MS(ESI): 571 (MH<sup>+</sup>).

### EXAMPLE 253

**Preparation of (2-chloroethyl)carbamic acid 2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yl ester**

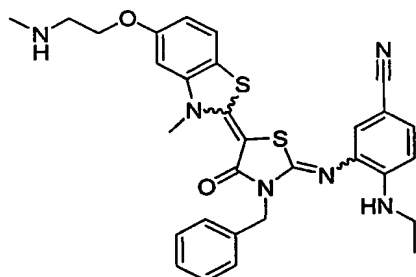


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The title compound was prepared in a manner similar to that described in Example 250 by replacing ethyl isocyanate with 2-chloroethylisocyanate. MS(ESI): 619 (MH<sup>+</sup>).

**EXAMPLE 254**

**5 Preparation of 3-{3-benzyl-5-[3-methyl-5-(2-methylaminoethoxy)-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile**



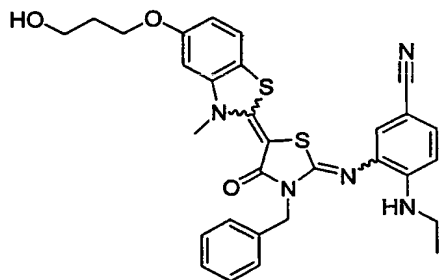
To the product of Example 57 (62 mg, 0.12 mmol) in anhydrous DMF  
10 (2 mL) were added 1,2-dibromoethane (100 mL, 10 equiv) and anhydrous K<sub>2</sub>CO<sub>3</sub> (166 mg, 10 equiv). The suspension was shaken overnight at 60°C in a sealed tube. After cooling, the reaction mixture was concentrated under reduced pressure, diluted with DCM and acetone, and filtered. The filtrate was concentrated to give a residue, which was purified by chromatography on  
15 silica gel, eluting with MeOH-DCM (1:19) to give a yellow solid, which was used in the next step without further purification.

The above material was dissolved in 2M solution of methylamine in THF (3 mL) and the solution was heated in a sealed tube for 40h at 60°C. After cooling, the product mixture was concentrated to give a residue, which  
20 was purified by chromatography on silica gel, eluting with MeOH-DCM (1:19 to 1:9) to give the title compound (10 mg). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.63 (1H, d), 7.28-7.39 (6H, m), 7.13 (1H, d), 7.03 (1H, d), 6.85 (1H, dd), 6.62 (1H, d), 5.13 (2H, s), 4.98 (1H, t), 4.12 (2H, t), 3.79 (3H, s), 3.05 (3H, m), 2.93 (2H, t), 2.3 (3H, s), 0.99 (3H, t); MS(ESI): 571 (MH<sup>+</sup>).

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## EXAMPLE 255

Preparation of 3-{3-benzyl-5-[5-(3-hydroxypropoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile

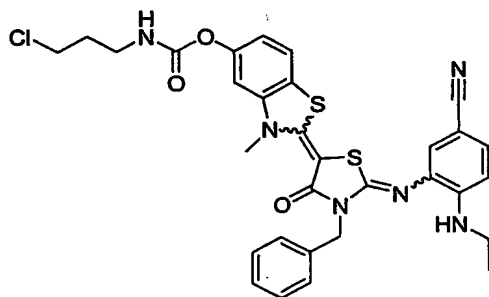


5

The title compound was prepared in a manner similar to that described in Example 59 by replacing 2-bromoethanol with 3-bromopropanol. MS(ESI): 572 (MH<sup>+</sup>).

## EXAMPLE 256

10 Preparation of (3-chloropropyl)carbamic acid 2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yl ester

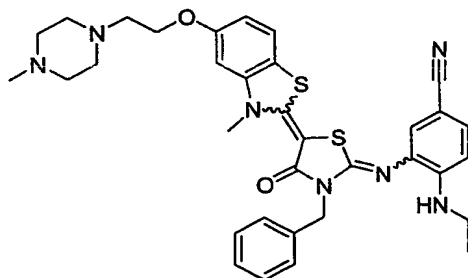


15 The title compound was prepared in a manner similar to that described in Example 250 by replacing ethyl isocyanate with 3-chloropropylisocyanate. MS(ESI): 633 (MH<sup>+</sup>).

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## EXAMPLE 257

Preparation of 3-(3-benzyl-5-{3-methyl-5-[2-(4-methylpiperazin-1-yl)-ethoxy]-3*H*-benzothiazol-2-ylidene}-4-oxothiazolidin-2-ylideneamino)-4-ethylaminobenzonitrile

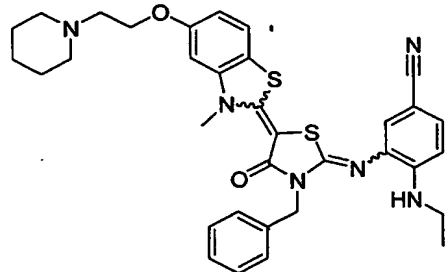


5

The title compound was prepared in a manner similar to that described in Example 60 by replacing morpholine with 1-methylpiperazine. MS(ESI): 640 (MH<sup>+</sup>).

## EXAMPLE 258

10 Preparation of 3-(3-benzyl-5-[3-methyl-5-(2-piperidin-4-ylethoxy)-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino)-4-ethylaminobenzonitrile

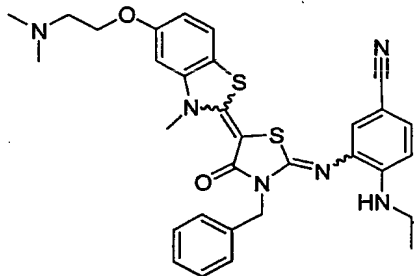


15 The title compound was prepared in a manner similar to that described in Example 60 by replacing morpholine with piperidine. MS(ESI): 625 (MH<sup>+</sup>).

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## EXAMPLE 259

Preparation of 3-{3-benzyl-5-[5-(2-dimethylaminoethoxy)-3-methyl-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile



5

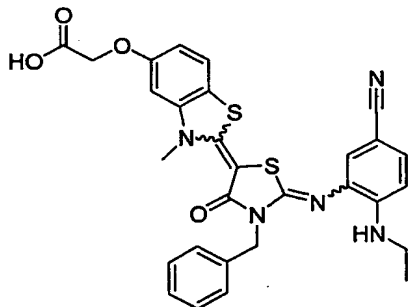
The title compound was prepared in a manner similar to that described in Example 60 by replacing morpholine with dimethylamine. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.43 (2H, m), 7.33 (1H, d), 7.29 (2H, m), 7.25-7.27 (5H, m), 7.20 (1H, d), 6.80 (1H, dd), 6.70 (1H, d), 6.49 (1H, d), 5.18 (2H, s), 4.22 (1H, t), 4.11 (2H, t), 3.77 (3H, s), 3.00 (2H, m), 2.75 (2H, t), 2.35 (6H, s), 1.02 (3H, t), MS(ESI): 585 (MH<sup>+</sup>).

10

## EXAMPLE 260

Preparation of {2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-ylloxy}acetic acid

15



To the product of Example 57 (158 mg, 0.31 mmol) in anhydrous DMF (5 mL) were added *tert*-butyl bromoacetate (460 μL, 10 equiv) and anhydrous K<sub>2</sub>CO<sub>3</sub> (425 mg, 10 equiv). The suspension was heated at 80°C under nitrogen for 16h. After cooling, resulting solids were removed by filtration.

20

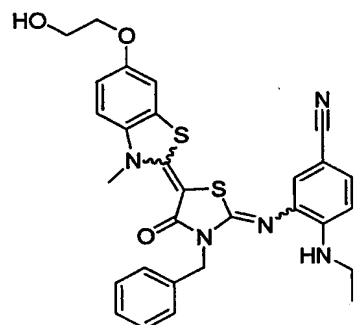
-291-

The filtrate was concentrated to give a residue, which was purified by chromatography on silica gel, eluting with MeOH-DCM (5:95) to give the product, which was used in the next step without further purification.

- The above product was dissolved in a 1:1 mixture of TFA/DCM (2 mL) and the solution was stirred for 1h at 20°C. Evaporation of solvent gave a residue, which was purified by chromatography on silica gel, eluting with MeOH-DCM (5:95) to give the title compound (35 mg, 75%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.61 (1H, m), 7.28-7.39 (6H, m), 7.13 (1H, d), 7.05 (1H, d), 6.82 (1H, dd), 6.62 (1H, d), 5.14 (2H, s), 4.95 (1H, t), 4.76 (2H, t), 3.79 (3H, s), 3.05 (2H, m), 0.99 (3H, t), MS(ESI): 572 (MH<sup>+</sup>).

#### EXAMPLE 261

**Preparation of 3-{3-benzyl-5-[6-(2-hydroxyethoxy)-3-methyl-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile**



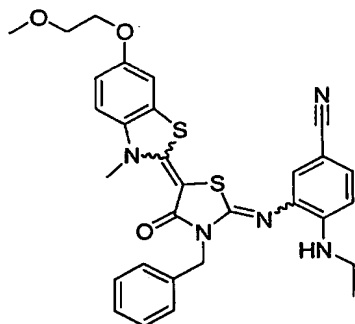
15

The title compound was prepared in a manner similar to that described in Example 59 by replacing the product of Example 57 with the product of Example 249. MS(ESI): 558 (MH<sup>+</sup>).

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**EXAMPLE 262**

**Preparation of 3-{3-benzyl-5-[6-(2-methoxyethoxy)-3-methyl-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile**

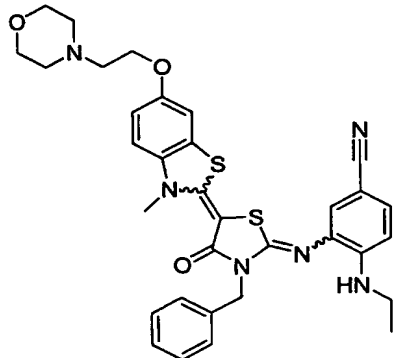


5

The title compound was prepared in the same manner as described in Example 261 in the presence of excess methyl *p*-toluenesulfonate. MS(ESI): 572 (MH<sup>+</sup>).

**EXAMPLE 263**

**10 Preparation of 3-{3-benzyl-5-[3-methyl-6-(2-morpholin-4-ylethoxy)-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile**



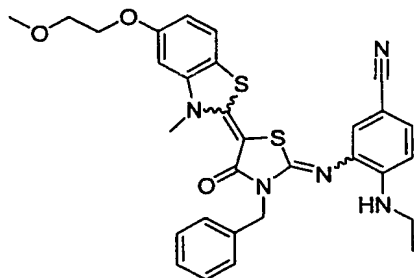
**15** The title compound was prepared in a manner similar to that described in Example 60 by replacing the product of Example 60 with the product of Example 261. MS(ESI): 627 (MH<sup>+</sup>).



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## EXAMPLE 264

Preparation of 3-{3-benzyl-5-[5-(2-methoxyethoxy)-3-methyl-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile



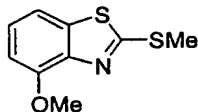
5

The title compound was prepared in the same manner as described in Example 59 in the presence of excess methyl *p*-toluenesulfonate. MS(ESI): 572 (MH<sup>+</sup>).

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## EXAMPLE 265

## A. Preparation of 4-methoxy-2-methylthiobenzothiazole

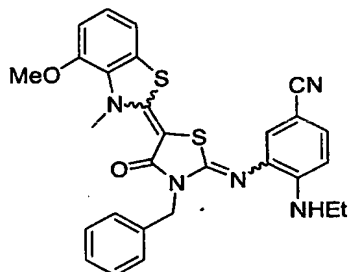


2-Amino-4-methoxybenzothiazole (3.6 g, 20 mmol) was dissolved in  
5 warm  $\text{H}_3\text{PO}_4$  (120 mL). The resulting homogeneous solution was cooled to  $-8^\circ\text{C}$ , and a solution of  $\text{NaNO}_2$  (8.28 g, 120 mmol) in  $\text{H}_2\text{O}$  (50 mL) was added dropwise with stirring such that the temperature was not allowed to rise above  $-4^\circ\text{C}$ . The resulting dark-red syrup was added slowly to  $\text{H}_3\text{PO}_2$  (50% in  $\text{H}_2\text{O}$ , 60 mL) at  $0^\circ\text{C}$  with stirring. After the addition was complete, the mixture was  
10 allowed to warm to ambient temperature until gas evolution had ceased. The solution was diluted with ice-water, cautiously neutralized with solid  $\text{Na}_2\text{CO}_3$ , and extracted with  $\text{CHCl}_3$  (3 x 200 mL). The combined extracts were washed with water (2 x 200 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure to give a red solid (2.87g), which was purified by chromatography on  
15 silica gel, eluting with EtOAc-Hex (0:100 to 30:70) to yield 4-methoxybenzothiazole (2.14 g, 65%) as a yellow solid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.90 (1H, s), 7.52 (1H, d), 7.38 (1H, t), 6.93 (1H, d), 4.06 (3H, s).

To a solution of 4-methoxybenzothiazole (495 mg, 3.0 mmol) in anhydrous THF (12 mL) at  $-78^\circ\text{C}$  was added BuLi (2.5 mL, 1.6M in hexanes,  
20 4.0 mmol) dropwise. The resulting red solution was stirred at  $-78^\circ\text{C}$  for 2h under  $\text{N}_2$ . Methyl disulfide (0.55 mL, 6.0 mmol) was added dropwise at  $-78^\circ\text{C}$  and the mixture was allowed to warm to ambient temperature overnight. The reaction mixture was combined with water and then extracted with EtOAc. The combined extracts were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and  
25 concentrated under reduced pressure to afford the title compound as a yellow oil (632 mg, 100%), which solidified upon standing and was used without purification.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.35 (1H, d), 7.24 (1H, q), 6.86 (1H, d), 4.06 (3H, s), 2.79 (3H, s).

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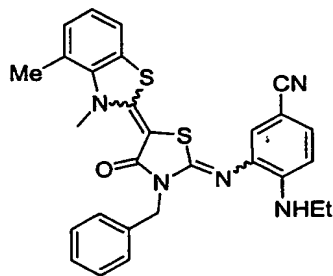
**B. Preparation of 3-{3-benzyl-5-[3-methyl-4-methoxy-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile**



- 5 To a suspension of the 4-methoxy-2-methylthiobenzothiazole (0.60 g, 2.8 mmol) in anhydrous anisole (8 mL) was added methyl *p*-toluenesulfonate (1.4 mL, 9.0 mmol) and the suspension was heated at 130°C for 3.5 h. After cooling to 20°C, MeCN (5 mL), 3-(3-benzyl-4-oxothiazolidin-2-ylideneamino)-4-ethylaminobenzonitrile (119 mg, 0.34 mmol) and TEA (2.0 mL, 14 mmol)
- 10 were added. The suspension was stirred for 5h at 80°C. After cooling to ambient temperature, yellow solids were collected by filtration, washed with MeCN and dried under high vacuum to afford the title compound (123 mg, 69%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.45-7.11 (9H, m), 6.88-6.85 (1H, m), 6.48 (1H, d), 5.17 (2H, s), 4.08 (3H, s), 3.92 (3H, s), 3.02-2.97 (2H, m), 1.02 (3H, t); MS
- 15 (ESI): 528 (MH<sup>+</sup>).

**EXAMPLE 266**

**Preparation of 3-{3-benzyl-5-[3-methyl-4-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile**



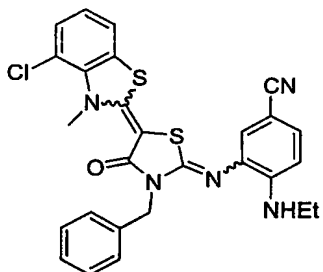
- 20 The title compound was prepared in a manner similar to that described in Example 265 by starting from 2-amino-4-methylbenzothiazole. <sup>1</sup>H-NMR

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(CDCl<sub>3</sub>):  $\delta$  7.46-7.06 (10H, m), 6.49 (1H, d), 5.17 (2H, s), 3.88 (3H, s), 3.04-2.97 (2H, m), 2.62 (3H, s), 1.03 (3H, t); MS (ESI): 512 (MH<sup>+</sup>).

**EXAMPLE 267**

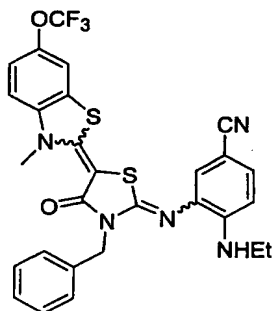
**Preparation of 3-{3-benzyl-5-[3-methyl-4-chloro-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile**



The title compound was prepared in a manner similar to that described in Example 265 by starting from 2-amino-4-chlorobenzothiazole. <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta$  7.45-7.08 (10H, m), 6.50 (1H, d), 5.17 (2H, s), 4.01 (3H, s), 3.04-2.98 (2H, m), 1.03 (3H, t); MS(ESI): 532 (MH<sup>+</sup>).

**EXAMPLE 268**

**Preparation of 3-{3-benzyl-5-[3-methyl-6-trifluoromethoxy-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile**

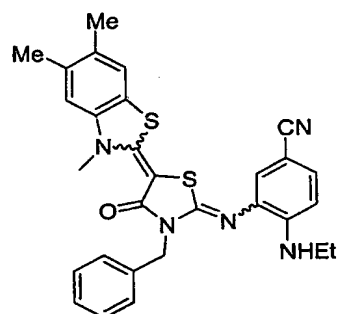


The title compound was prepared in a manner similar to that described in Example 265 by starting from 2-amino-6-(trifluoromethoxy)benzothiazole. <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta$  7.44-7.18 (9H, m), 7.06 (1H, d), 6.49 (1H, d), 5.17 (2H, s), 3.81 (3H, s), 3.04-2.97 (2H, m), 1.03 (3H, t); MS(ESI): 582 (MH<sup>+</sup>).

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## EXAMPLE 269

Preparation of 3-[3-benzyl-5-(3,5,6-trimethyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile

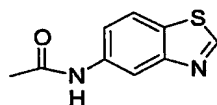


- 5 The title compound was prepared in a manner similar to that described in Example 265 by starting from 2-amino-5,6-dimethylbenzothiazole. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.44-7.20 (8H, m), 6.90 (1H, s), 6.48 (1H, d), 5.17 (2H, s), 3.80 (3H, s), 3.03-2.97 (2H, m), 2.35 (3H, s), 2.31 (3H, s), 1.02 (3H, t); MS(ESI): 526 (MH<sup>+</sup>).

10

## EXAMPLE 270

## A. Preparation of 5-acetamidobenzothiazole



- 15 To a stirred solution of 4-chloro-3-nitroaniline (17.3 g, 100 mmol) in DCM (150 mL) was added dropwise acetic anhydride (14 mL, 150 mmol) at ambient temperature. The mixture was stirred at ambient temperature for 2.5h. The solvent was removed in vacuo, and Et<sub>2</sub>O was added to the residue. The precipitate was collected by filtration, washed with Et<sub>2</sub>O, and dried in vacuo to give N-(4-chloro-3-nitrophenyl)acetamide (20.7 g, 96%), which was used without further purification.

- 20 A suspension of the above compound (13.8 g, 64.3 mmol) and Na<sub>2</sub>S·9H<sub>2</sub>O (18.6 g, 77.2 mmol) in DMF (100 mL) was stirred at ambient temperature under N<sub>2</sub> overnight. The reaction mixture was filtered, and the filtrate was diluted with water (400 mL) and then acidified with conc HCl to pH 3. The resulting yellow solids were collected by filtration, washed with water

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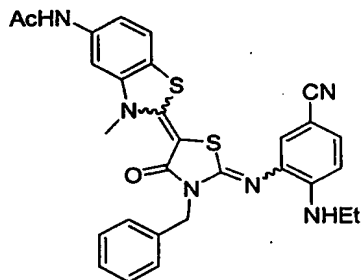
and dried under high vacuum to afford 4'-mercapto-3'-nitroacetanilide (12.0 g, 88%).

A suspension of 4'-mercapto-3'-nitroacetanilide (3.0 g, 14 mmol) and 10% Pd/C (0.6 g) in MeOH (200 mL) was hydrogenated at 60psi overnight.

- 5 The catalyst was removed by filtration, and the filtrate was concentrated to give 3'-amino-4'-mercaptoacetanilide (2.5 g, 13 mmol), which was used in the next reaction immediately.

- To a solution of intermediate 3'-amino-4'-mercaptoacetanilide in HOAc (50 mL) was added ethoxymethylene malononitrile (1.95 g, 16 mmol) and the  
10 resulting mixture was refluxed at 125°C for 5h. After cooling, the product mixture was concentrated under reduced pressure, and the residue was partitioned between satd aqueous NaHCO<sub>3</sub> and EtOAc. The aqueous phase was extracted with EtOAc, and the combined extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The residue was purified by  
15 chromatography on silica gel, eluting with EtOAc-Hex (0:100 to 50:50) to give the title compound (508 mg, 17%) as a yellow solid. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 9.35 (1H, s), 8.53 (1H, s), 8.10 (1H, d), 7.63 (1H, d), 2.15 (3H, s).

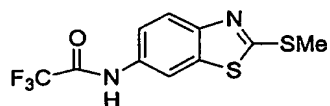
- B. Preparation of 3-[3-benzyl-5-(3-methyl-5-acetamido-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile**  
20



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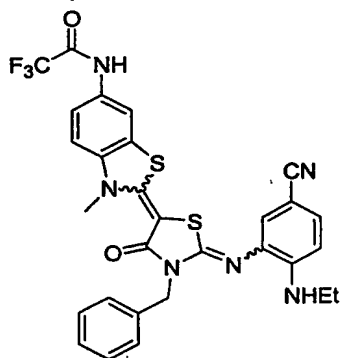
## EXAMPLE 271

## A. Preparation of 2-methylthio-6-(trifluoroacetoamido)benzothiazole



To a suspension of 6-amino-2-mercaptobenzothiazole (550 mg, 3.0 mmol) in anhydrous MeCN (15 mL) was added TEA (0.9 mL) and methyl *p*-toluenesulfonate (0.45 mL, 3.0 mmol) at ambient temperature. The mixture turned to a clear solution after a few minutes and was stirred at ambient temperature for 3h. To the above solution was added dropwise TFAA (0.65 mL, 4.6 mmol). After 12h the solution was concentrated under reduced pressure, diluted with EtOAc, washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The resulting residue was purified by chromatography on silica gel, eluting with EtOAc-Hex (0:100 to 10:90) to give the title compound (575 mg, 66%) as a white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.31 (1H, d), 7.99 (1H, br s), 7.84 (1H, d), 7.35 (1H, dd), 2.80 (3H, s).

B. Preparation of N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-6-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yl}-2,2,2-trifluoroacetamide

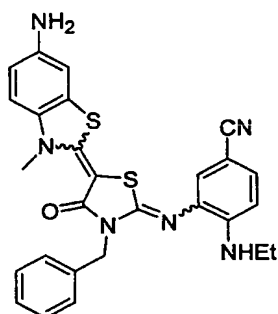


The title compound was prepared in a manner similar to that described in Example 265 by starting with 2-methylthio-6-(trifluoroacetamido)benzothiazole. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ 7.82 (1H, d), 7.40-7.06 (8H, m), 6.90 (1H, d), 6.48 (1H, d), 6.40 (1H, d), 4.89 (2H, s), 3.57 (3H, s), 2.83 (2H, m), 0.77 (3H, t); MS(ESI): 609 (MH<sup>+</sup>).

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## EXAMPLE 272

Preparation of 3-[5-(6-amino-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile



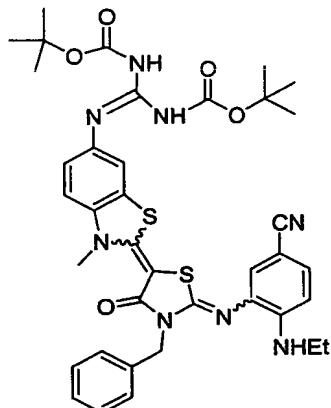
- 5 To the product of Example 271 (400 mg, 0.66 mmol) in a mixture of MeOH/H<sub>2</sub>O (12 mL, 5:1 v/v) was added potassium carbonate (553 mg, 4.0 mmol). The reaction mixture was stirred at 60°C for 16h, and then concentrated under reduced pressure. The resulting residue was partitioned between CHCl<sub>3</sub> and water. The aqueous phase was extracted with CHCl<sub>3</sub>,
- 10 and the combined extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to give the title compound (326 mg, 97%) as a yellow solid. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ 7.40-7.28 (6H, m), 7.15-7.13 (2H, m), 6.88 (1H, d), 6.66-6.61 (2H, m), 5.23 (2H, br s), 5.11 (2H, s), 3.75 (3H, s), 3.09-3.02 (2H, m), 1.01 (3H, t); MS(ESI): 513 (MH<sup>+</sup>).



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## EXAMPLE 273

Preparation of N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}-N',N''-di(*tert*-butoxycarbonyl)guanidine



5

To a stirred mixture of the product of Example 272 (77 mg, 0.15 mmol), N, N'-di(*tert*-butoxycarbonyl)thiourea (50 mg, 0.18 mmol) and TEA (70  $\mu$ L, 0.5 mmol) in anhydrous DMF (1.5 mL) at 0°C was added HgCl<sub>2</sub> (49 mg, 0.18 mmol). The resulting mixture was stirred at 0°C for 30min, then at ambient temperature overnight. The mixture was diluted with CHCl<sub>3</sub>, washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The residue was purified by chromatography on silica gel, eluting with MeOH-DCM (0:100 to 20:80) to afford the title compound (98 mg, 87%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta$  11.62 (1H, br s), 10.43 (1H, br s), 8.02 (2H, m), 7.45-7.20 (7H, m), 7.02 (1H, d), 6.49 (1H, t), 5.16 (2H, s), 3.82 (3H, s), 3.04-2.96 (2H, m), 1.43 (9H, s), 1.35 (9H, s), 1.02 (3H, t); MS(ESI): 756 (MH<sup>+</sup>).

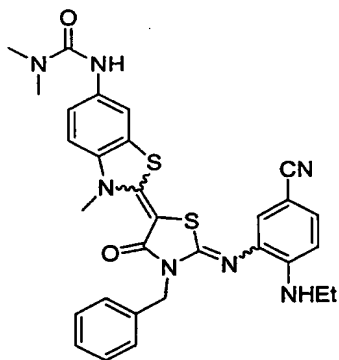
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## EXAMPLE 274

**Preparation of 2-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}-1,1-dimethylurea**



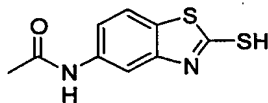
5

To the product of Example 272 (89 mg, 0.174 mmol) in anhydrous  $\text{CHCl}_3$  (5 mL) were added TEA (0.3 mL, 2.4 mmol) and dimethylcarbamy chloride (0.2 mL, 2.0 mmol). The resulting mixture was stirred at ambient temperature overnight. After diluting with  $\text{CHCl}_3$ , the mixture was washed with satd  $\text{NaHCO}_3$  and brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated in vacuo. The residue was purified by chromatography on silica gel, eluting with MeOH-DCM (0:100 to 5:95) to afford the title compound (48 mg, 47%).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.70 (1H, d), 7.44-7.26 (8H, m), 7.20 (1H, d), 7.00 (1H, d), 6.48 (1H, d), 6.38 (1H, s), 5.16 (2H, s), 3.79 (3H, s), 3.06 (6H, s), 3.05-2.97 (2H, m), 1.02 (3H, t); MS(ESI): 584( $\text{MH}^+$ ).

15

## EXAMPLE 275

## A. Preparation of 5-acetamido-2-mercaptobenzothiazole



To a stirred solution of 4-chloro-3-nitroaniline (51.8 g, 0.36 mol) in anhydrous DCM (300 mL) was added dropwise acetic anhydride (45 mL, 0.48mol) at room temperature, and the resulting solution was stirred at room temperature for 3h. The solvent was removed in vacuo, and  $\text{Et}_2\text{O}$  was added to the residue. The precipitates were collected by filtration, washed

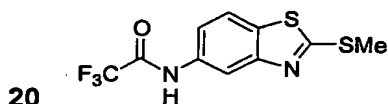
20

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thoroughly with Et<sub>2</sub>O, and dried under high vacuum to give 4'-chloro-3'-nitroacetanilide (78.7 g, 100%).

- 5 A mixture of Na<sub>2</sub>S·9H<sub>2</sub>O (65 g, 0.28 mol), sulfur (25 g, 0.78 mol) and water (150 mL) were heated with stirring at 90°C for 10min, and then poured into a flask charged with the above 4'-chloro-3'-nitroacetanilide (21.5 g, 0.10 mol). The resulting mixture was heated at 80°C for 10min, and then CS<sub>2</sub> (12 mL, 0.2 mol) was added dropwise while maintaining a gentle reflux. The resulting mixture was heated at 90°C for 7h. The solids were collected by filtration, washed with water and dilute HCl solution. The solids were taken up
- 10 in water, and the solution was made alkaline with solid NaOH. The solution was filtered, and the filtrate was acidified with conc HCl. The precipitates were collected by filtration, washed with water, and dried under high vacuum. The crude product was suspended in cold water (200 mL) and solid Na<sub>2</sub>CO<sub>3</sub> was added to obtain pH 13. Dimethyl sulfate was added to the above milky
- 15 solution, and the resulting mixture was stirred at ambient temperature for 3h. The solids were collected by filtration, washed with water, and dried under high vacuum to yield the title compound (12.4 g, 55%).

**B. Preparation of 2-methylthio-5-(2,2,2-trifluoroacetamido)benzothiazole**



- A suspension of 5-acetamido-2-mercaptobenzothiazole (12.9 g, 54 mmol) in a mixture of conc HCl (30 mL) and water (60 mL) was heated at reflux for 3h. After cooling, the mixture was extracted with CHCl<sub>3</sub>, and the aqueous phase was diluted with ice-water. To the aqueous layer was added
- 25 portionwise solid NaOH to achieve pH 6, and then solid K<sub>2</sub>CO<sub>3</sub> to obtain pH 8. The precipitates were collected by filtration, washed with water, and dried under high vacuum to yield 5-amino-2-methylthiobenzothiazole (7.65 g, 72%).

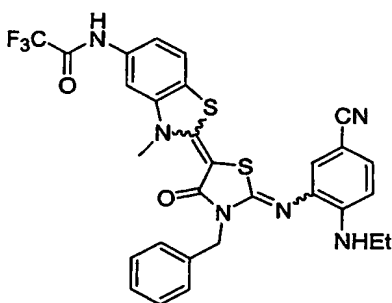
- To a stirred solution of 5-amino-2-methylthiobenzothiazole (3.93 g, 20 mmol) in anhydrous MeCN were added dropwise at 0°C TFAA (4.0 mL, 28
- 30 mmol) and TEA (5 mL, 36 mmol) under N<sub>2</sub>. The mixture was stirred at room

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temperature for 3h. The solvent was removed in vacuo, and the residue was taken up in EtOAc, washed with water and brine, dried with Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The crude material was purified by chromatography on silica gel, eluting with EtOAc-Hex (0:100 to 20:80) to afford the title

- 5 compound (3.9 g, 67% ) as a pale white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.10 (1H, d), 7.98 (1H, br s), 7.75 (1H, d), 7.53-7.51 (1H, dd), 2.80 (3H, s).

**C. Preparation of N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yl}-2,2,2-trifluoroacetamide**



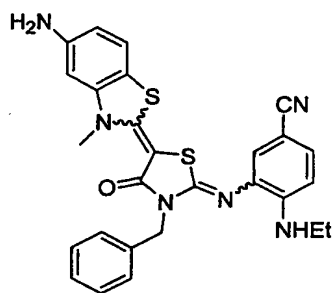
10

The title compound was prepared from 2-methylthio-5-trifluoroacetoamido-benzothiazole in a manner similar to that described in Example 265. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ 7.82 (1H, d), 7.56-7.26 (8H, m), 7.16 (1H, d), 6.51 (1H, d), 5.16 (2H, s), 3.83 (3H, s), 3.03-2.96 (2H, m), 1.02 (3H, t); MS(ESI): 609 (MH<sup>+</sup>).

15

**EXAMPLE 276**

**Preparation of 3-[5-(5-amino-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile**

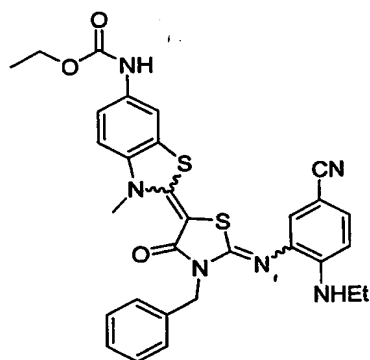


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The title compound was prepared from the product of Example 275 in a manner similar to that described in Example 272. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ 8.38 (1H, s), 7.47-7.36 (6H, m), 7.21 (1H, d), 6.69 (1H, d), 6.61-6.56 (2H, m), 4.45 (2H, br s), 5.18 (2H, s), 3.78 (3H, s), 3.12 (2H, m), 1.06 (3H, t) MS(ESI): 513 (MH<sup>+</sup>).

**EXAMPLE 277**

**Preparation of {2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}carbamic acid ethyl ester**



10

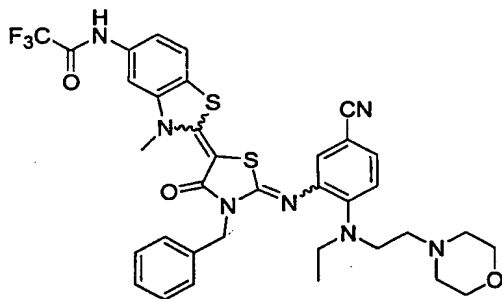
The title compound was prepared in a manner similar to that described in Example 274 by replacing dimethylcarbonyl chloride with ethyl chloroformate. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ 9.64 (1H, s), 7.75 (1H, d), 7.29-7.16 (8H, m), 7.02 (1H, d), 6.51 (1H, d), 5.00 (2H, s), 4.04-3.98 (2H, q), 3.68 (3H, s), 2.97-2.91 (2H, m), 1.26 (3H, t), 0.88 (3H, t); MS(ESI): 585 (MH<sup>+</sup>).

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## EXAMPLE 278

Preparation of N-[2-(3-benzyl-2-{5-cyano-2-[4-(2-morpholinoethyl)amino]phenylimino}-4-oxothiazolidin-5-ylidene)-3-methyl-2,3-dihydrobenzothiazol-6-yl]-2,2,2-trifluoroacetamide



5

Sodium hydride (8 mg, 60% w/w in mineral oil, 0.2 mmol) was added at 0°C to a stirred solution of the product of Example 271 (52 mg, 0.1 mmol) in anhydrous DMF under N<sub>2</sub>. The mixture was stirred at 0°C for 5min, then at ambient temperature for 15min. 4-(2-Chloroethyl)morpholine hydrochloride (24 mg, 0.15 mmol) was added to the above red solution at 0°C, and the mixture was stirred at ambient temperature under N<sub>2</sub> for 21h. The reaction mixture was diluted with CHCl<sub>3</sub>, washed thoroughly with water, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with MeOH-DCM (0:100 to 20:80) to afford the title compound (42mg, 58%) as a yellow solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 8.98 (1H, br s), 7.92 (1H, s), 7.68 (1H, s), 7.51-7.22 (7H, m), 6.81 (1H, d), 5.12 (2H, s), 4.04 (2H, m), 3.64 (5H, m), 3.36 (2H, m), 2.54-2.17 (8H, m), 1.26 (3H, m); MS(ESI): 722 (MH<sup>+</sup>).

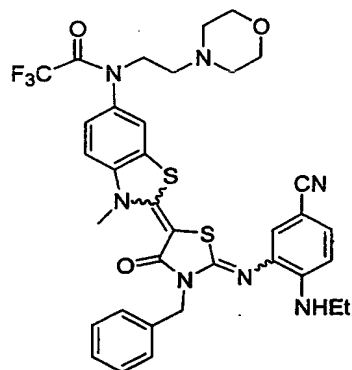
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## EXAMPLE 279

Preparation of N-(2-[3-benzyl-2-(5-cyano-2-ethylaminophenylidene)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl)-2,2,2-trifluoro-N-(2-morpholin-4-ylethyl)acetamide



To the product of Example 271 (65 mg, 0.11 mmol) in anhydrous DMF were added 4-(2-chloroethyl)morpholine hydrochloride (50 mg, 0.3 mmol),  $K_2CO_3$  (30 mg, 0.21 mmol) and KI (10 mg). The reaction mixture was heated at 90°C for 30h, cooled, and diluted with  $CHCl_3$ . The solution was washed with water, dried over  $Na_2SO_4$ , and concentrated in vacuo. The crude material was purified by chromatography on silica gel, eluting with MeOH-DCM (0:100 to 20:80) to afford the title compound (72 mg, 94%) as a yellow solid.  $^1H$ -NMR ( $CDCl_3$ ):  $\delta$  7.51 (1H, s), 7.44-7.42 (2H, m), 7.38-7.28 (5H, m), 7.19 (1H, d), 7.09 (1H, d), 5.18 (2H, s), 4.21 (2H, br s), 3.85 (3H, s), 3.68 (4H, br s), 3.05-2.96 (2H, m), 2.52-2.45 (6H, m), 1.03 (3H, t); MS(ESI): 722 ( $MH^+$ ).

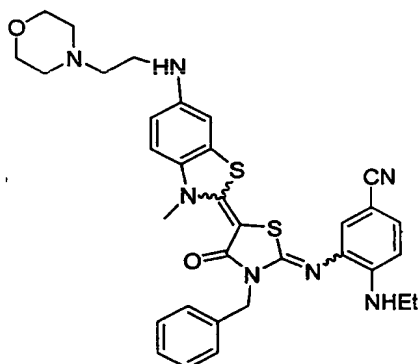
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## EXAMPLE 280

Preparation of 3-{3-benzyl-5-[3-methyl-6-(2-morpholin-4-yl-ethylamino)-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile



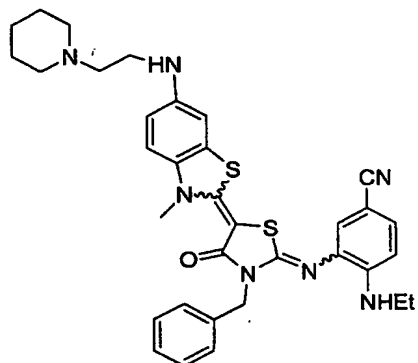
5

The title compound was prepared from the product of Example 279 in a manner similar to that described in Example 272. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.44-7.21 (7H, m), 6.93 (1H, d), 6.78 (1H, d), 6.65 (1H, m), 6.48 (1H, d), 5.17 (2H, s), 3.81 (3H, s), 3.80-3.74 (4H, m), 3.20-3.17 (2H, m), 3.03-2.96 (2H, m), 2.67 (2H, br s), 2.49 (4H, br s), 1.02 (3H, t); MS(ESI): 626 (MH<sup>+</sup>).

10

## EXAMPLE 281

Preparation of 3-{3-benzyl-5-[3-methyl-6-(2-piperidin-1-yl-ethylamino)-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile



15

The title compound was prepared in a manner similar to that described in Examples 279 and 280 by replacing 4-(2-chloroethyl)morpholine



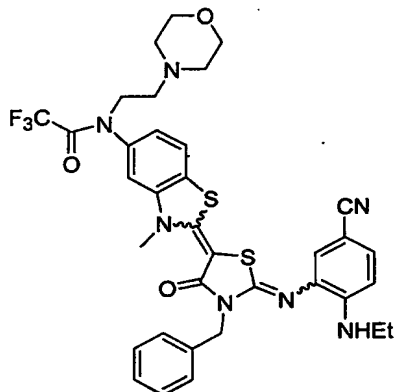
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hydrochloride with 4-(2-chloroethyl)piperidine hydrochloride.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.44-7.19 (7H, m), 6.93 (1H, d), 6.77-6.71 (2H, m), 6.48 (1H, d), 5.16 (2H, s), 3.77 (3H, s), 3.28 (2H, br s), 3.03-2.96 (2H, m), 2.81 (2H, br s), 2.48 (2H, br s), 2.04 (4H, br s), 1.02 (3H, t); MS(ESI): 624 ( $\text{MH}^+$ ).

5

**EXAMPLE 282**

**Preparation of N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yl}-2,2,2-trifluoro-N-(2-morpholin-4ylethyl)acetamide**



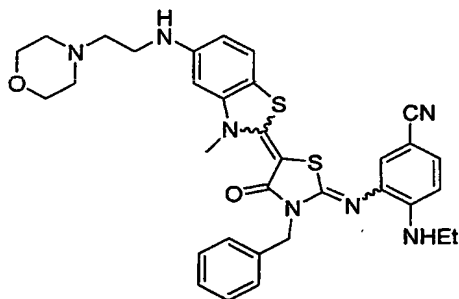
10

The title compound was prepared from the product of Example 275 in a manner similar to that described in Example 279.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.54 (1H, d), 7.44-7.11 (9H, m), 6.50 (1H, d), 5.18 (2H, s), 3.95 (2H, m), 3.79 (3H, s), 3.70 (4H, m), 3.04-2.98 (2H, m), 2.49 (6H, m), 1.03 (3H, t); MS(ESI): 722 ( $\text{MH}^+$ ).

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## EXAMPLE 283

Preparation of 3-{3-benzyl-5-[3-methyl-5-(2-morpholin-4-yl-ethylamino)-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile



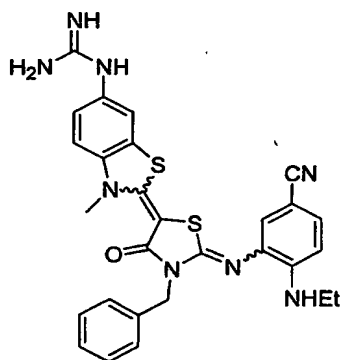
5

The title compound was prepared from the product of Example 282 in a manner similar to that described in Example 272. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.54 (1H, d), 7.44-7.11 (9H, m), 6.50 (1H, d), 5.18 (2H, s), 3.80 (2H, s), 3.70 (4H, br s), 3.04-2.98 (2H, m), 2.49 (6H, br s), 1.03 (3H, t); MS(ESI): 626 (MH<sup>+</sup>).

10

## EXAMPLE 284

Preparation of N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}guanidine



15

To a stirred solution of the product of Example 273 (116 mg, 0.15 mmol) in anhydrous DCM (6 mL) was added TFA (3 mL) at 0°C. The reaction mixture was stirred at 0°C for 30min, then at ambient temperature for 14h. The solvent was removed in vacuo, and the residue was purified by reverse-

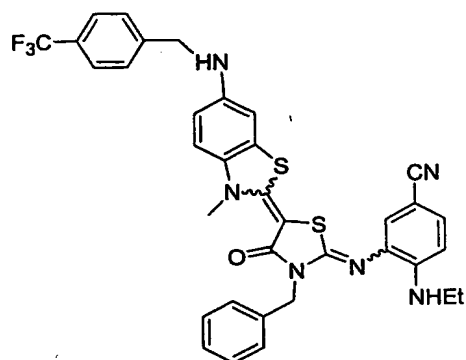
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phase HPLC (C18 column), eluting with 0.05% TFA in MeCN-H<sub>2</sub>O (1:9 to 9:1) to afford the title compound (25 mg, 30%) as a yellow solid. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ 9.65 (1H, s), 7.72 (1H, d), 7.48 (1H, d), 7.41-7.25 (8H, m), 7.15 (1H, d), 6.65 (1H, d), 5.14 (2H, s), 3.84 (3H, s), 3.07 (2H, m), 1.01 (3H, t); MS(ESI):

5 555 (MH<sup>+</sup>).

#### EXAMPLE 285

**Preparation of 3-{3-benzyl-5-[3-methyl-6-(4-trifluoromethylbenzylamino)-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile**



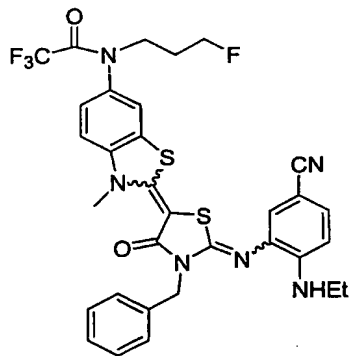
The title compound was prepared in a manner similar to that described in Examples 279 and 280 by replacing 4-(2-chloroethyl)morpholine hydrochloride with 4-(trifluoromethyl)benzyl bromide. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ

7.69 (2H, d), 7.58 (2H, d), 7.38-7.32 (6H, m), 7.17 (1H, d), 7.14 (1H, d), 6.94  
15 (1H, d), 6.63 (1H, dd), 6.61 (1H, d), 5.10 (2H, s), 4.40 (2H, s), 3.73 (3H, s),  
3.05 (2H, m), 1.00 (3H, t); MS(ESI): 671 (MH<sup>+</sup>).

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## EXAMPLE 286

Preparation of N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}-N-(3-fluoropropyl)-2,2,2-trifluoroacetamide



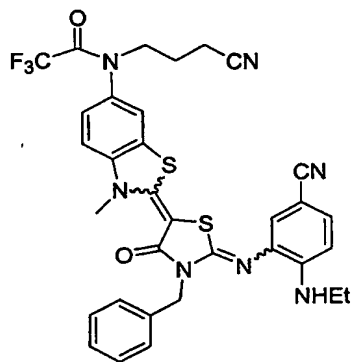
The title compound was prepared in a manner similar to that described in Example 279 by replacing 4-(2-chloroethyl)morpholine hydrochloride with 1-bromo-3-fluoropropane. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.44-7.19 (9H, m), 7.10 (1H, d), 6.50 (1H, d), 5.18 (2H, s), 4.60 (1H, m), 4.48 (1H, m), 4.20 (1H, m), 3.91 (1H, m), 3.83 (3H, s), 3.01 (2H, m), 2.09-1.99 (2H, m), 1.03 (3H, t); MS(ESI): 669 (MH<sup>+</sup>).

10

## EXAMPLE 287

Preparation of N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}-N-(3-cyanopropyl)-2,2,2-trifluoroacetamide

15

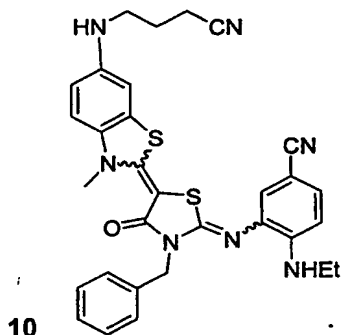


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The title compound was prepared in a manner similar to that described in Example 279 by replacing 4-(2-chloroethyl)morpholine hydrochloride with 4-bromobutyronitrile. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.44-7.19 (9H, m), 7.11 91H, d), 6.51 91H, d), 5.19 (2H, s), 3.86 (3H, s), 3.85-3.77 (2H, m), 3.05-2.98 (2H, m), 2.53-2.44 (2H, m), 2.04-1.88 (2H, m), 1.03 (3H, t); MS(ESI): 676 (MH<sup>+</sup>).

**EXAMPLE 288**

**Preparation of 3-{3-benzyl-5-[6-(3-cyanopropylamino)-3-methyl-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-(ethylamino)benzonitrile**

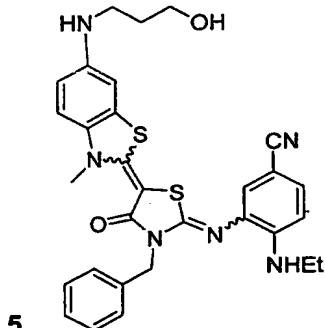


The title compound was prepared from the product of Example 287 in a manner similar to that described in Example 272. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.44-7.20 (7H, m), 6.94 (1H, d), 6.77 (1H, d), 6.65 (1H, dd), 6.48 (1H, d), 5.17 (2H, s), 3.77 (3H, s), 3.34 (2H, m), 3.01 (2H, m), 2.49 (2H, m), 2.01 (2H, m), 1.02 (3H, t); MS(ESI): 580 (MH<sup>+</sup>).

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## EXAMPLE 289

Preparation of 3-{3-benzyl-5-[6-(3-hydroxypropylamino)-3-methyl-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-(ethylamino)benzonitrile



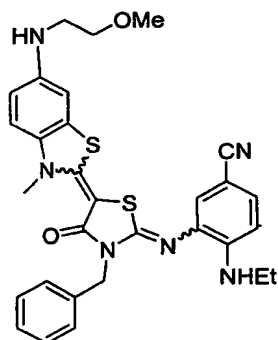
The title compound was prepared in a manner similar to that described in Examples 279 and 280 by replacing 4-(2-chloroethyl)morpholine hydrochloride with 3-bromopropanol. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.44- 7.21 (8H, m), 6.93 (1H, d), 6.79 (1H, d), 6.65 (1H, dd), 6.48 (1H, d), 5.17 (2H, s), 3.85 (2H, m), 3.77 (3H, s), 3.30 (2H, t), 3.01 (2H, m), 1.92 (2H, m), 1.02 (3H, t); MS(ESI): 571 (MH<sup>+</sup>).

10

## EXAMPLE 290

Preparation of 3-{3-benzyl-5-[6-(2-methoxyethylamino)-3-methyl-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-(ethylamino)benzonitrile

15



The title compound was prepared in a manner similar to that described in Examples 279 and 280 by replacing 4-(2-chloroethyl)morpholine

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hydrochloride with 2- bromoethyl methyl ether.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.44-7.21 (7H, m), 6.93 (1H, d), 6.79 (1H, d), 6.66 (1H, dd), 6.48 (1H, d), 5.17 (2H, s), 3.77 (3H, s), 3.63 (2H, m), 3.41 (3H, s), 3.30 (2H, m), 3.00 (2H, m), 1.02 (3H, t); MS(ESI): 571 ( $\text{MH}^+$ ).

5

**EXAMPLE 291****In Vivo studies**

In order to evaluate direct regulation of key target genes by the compounds of the invention, animals are administered a single oral dose of the test compound and tissues collected at six or fifteen hours after dose.

- 10 Male C57BL/6 mice ( $n=8$ ) are dosed by oral gavage with vehicle or compound. At six and fifteen hours after the dose, animals are bled via the retro orbital sinus for plasma collection. Animals are then euthanized and tissues, such as liver and intestinal mucosa are collected and snap frozen for further analysis. Plasma is analyzed for lipid parameters, such as total
- 15 cholesterol, HDL cholesterol and triglyceride levels. RNA is extracted for frozen tissues and can be analyzed by quantitative real time PCR for regulation of key target genes. To identify specificity of target gene regulation by FXR, knock out mice ( $\text{FXR}^{-/-}$ ) and C57BL/6 wild-type controls maybe used in this same protocol.

20

**Plasma Lipid Evaluation**

- To compare the effects of compounds on plasma cholesterol and triglycerides, animals are dosed with compound for one week and plasma lipid levels are monitored throughout the study. Male C57BL/6 mice ( $n=8$ ) are dosed daily by oral gavage with vehicle or compound. Plasma samples are
- 25 taken on day -1 (in order to group animals), day 1, 3, and 7. Samples are collected three hours after the daily dose. On day 7 of the study, following plasma collection, animals are euthanized and tissues, such as liver and intestinal mucosa are collected and snap frozen for further analysis. Plasma is analyzed for lipid parameters, such as total cholesterol, HDL cholesterol
- 30 and triglyceride levels. RNA is extracted for frozen tissues and can be analyzed by quantitative real time PCR for regulation of key target genes. To

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identify specificity of target gene regulation by FXR knockout mice and C57BL/6 wild-type controls maybe used in this same protocol.

#### **Cholesterol Absorption**

- Evaluation of compounds to inhibit cholesterol absorption is done via
- 5 measurement of labeled cholesterol in feces. Male A129 mice (n=7) are dosed daily by oral gavage with vehicle or compound for 7 days. On day 7 of the study, animals are administered [<sup>14</sup>C]-cholesterol and [<sup>3</sup>H]-sitostanol by oral gavage. Animals are individually housed on wire racks for the next 24 hours in order to collect feces. Feces are then dried and ground to a fine
- 10 powder. Labeled cholesterol and sitostanol are extracted from the feces and ratios of the two are counted on a liquid scintillation counter in order to evaluate the amount of cholesterol absorbed by the individual animal.

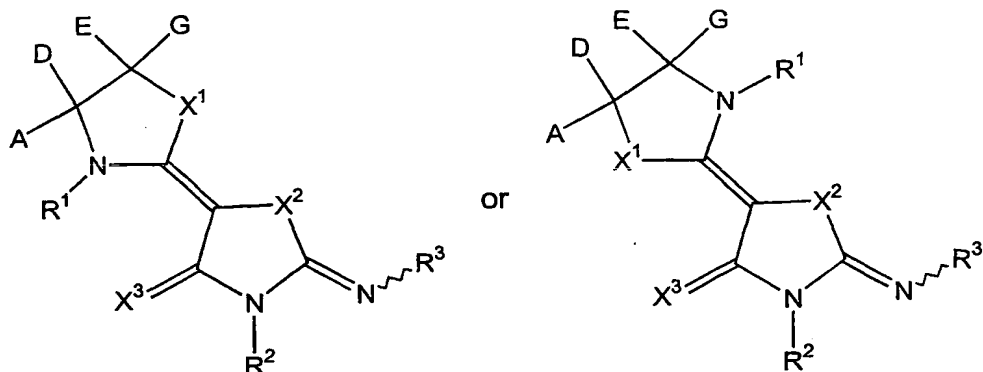
- Since modifications will be apparent to those of skill in this art, it is
- 15 intended that the subject matter claimed herein be limited only by the scope of the appended claims.



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**WHAT IS CLAIMED IS:**

1. A compound that has formulae I:



or a pharmaceutically acceptable derivative thereof, wherein:

5  $X^1$ ,  $X^2$  and  $X^3$  are selected from (i) or (ii) as follows:

(i)  $X^1$ ,  $X^2$  and  $X^3$  are each independently S, O or  $NR^5$ ; or

(ii)  $X^1$  is  $-CR^8=CR^9-$ , where  $R^8$  and  $R^9$  are each independently

selected from hydrogen, substituted or unsubstituted alkyl, substituted or  
 10 unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or  
 unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted  
 or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl,  
 substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,  
 substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl,  
 halo, pseudohalo,  $OR^{10}$ ,  $NR^{14}R^{15}$  and  $C(=J)R^{13}$ ; and  $X^2$  and  $X^3$  are each  
 15 independently S, O or  $NR^5$ ;

$R^1$  is substituted or unsubstituted alkyl;

$R^2$  is substituted or unsubstituted aralkyl, substituted or unsubstituted  
 aryl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkyl,  
 substituted or unsubstituted cycloalkyl, substituted or unsubstituted  
 20 heteroaralkyl, or substituted or unsubstituted heterocyclalkyl;

$R^3$  is substituted or unsubstituted heteroaryl, substituted or  
 unsubstituted aryl, or substituted or unsubstituted aralkyl;

A and G are selected from (i), (ii) or (iii) as follows:

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(i) A and G are each independently selected from hydrogen, substituted or unsubstituted aryl, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy carbonyl, hydroxycarbonyl, and substituted or unsubstituted alkyl carbonyl, where the substituents, when present, are each  
5 selected independently from  $Q^1$ , with the proviso that when  $R^1$  is Et,  $X^1$  and  $X^2$  are S,  $X^3$  is O,  $R^3$  is 3-methylphenyl,  $R^2$  is allyl, and D and E form a bond, then A and G are not both methyl; or

(ii) A and G together form substituted or unsubstituted alkylene, or substituted or unsubstituted azaalkylene, where the substituents, when  
10 present, are each selected independently from  $Q^1$ ; or

(iii) A and G together form substituted butadienyl, where there are 1 to 4 substituents selected from  $Q^1$ , with the provisos that (a) when  $X^1$  and  $X^2$  are S and  $X^3$  is O, then the resulting benzothiazolyl group is not mono-substituted at the 5-position with methoxy or chloro or at the 6-position with  
15 methoxy, and (b) when  $X^1$  is  $-CR^8=CR^9-$ ,  $X^2$  is S and  $X^3$  is O, then the resulting quinolyl group is not mono-substituted at the 6-position with methoxy or methyl;

D and E are each hydrogen, or together form a bond; and

$R^5$  is hydrogen, substituted or unsubstituted alkyl, substituted or  
20 unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl,  
25 halo, pseudohalo,  $OR^{10}$ ,  $SR^{10}$ ,  $S(=O)R^{13}$ ,  $S(=O)_2R^{13}$ ,  $NR^{14}R^{15}$  or  $C(=J)R^{13}$ ;

$R^{10}$  is hydrogen, substituted or unsubstituted alkyl, substituted or  
unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or  
unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted  
or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl,  
30 substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,

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substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl or  $C(=J)R^{13}$ ;

J is O, S or  $NR^{14}$ ;

$R^{13}$  is selected from hydrogen, substituted or unsubstituted alkyl,

- 5 substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, pseudohalo,  $OR^{16}$  and  $NR^{14}R^{15}$ ;

$R^{14}$ ,  $R^{15}$  and  $R^{16}$  are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl;

wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl,

- 15 cycloalkylalkyl, heterocyclalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl moieties of  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^5$ ,  $R^{10}$ ,  $R^{13}$ , A and G, when substituted, are substituted with one or more substituents each independently selected from  $Q^1$ , where  $Q^1$  is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, 25 alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclaloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, 30 aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, aralkoxycarbonyloxy,

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- aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, imino, hydroxyimino, alkoxyimino, aralkoxyimino, arylazo, haloalkylcarbonylamino, aminothiocabonyl, alkylaminothiocabonyl,
- 10 arylaminothiocabonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminomalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino,
- 15 aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclisulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio,
- 20 hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxyulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl,
- 25 hydroxysulfonyl, alkoxyulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two  $Q^1$  groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy, thioalkylenoxy or alkylenedithioxy; or two  $Q^1$  groups, which substitute the same atom, together
- 30 form alkylene;

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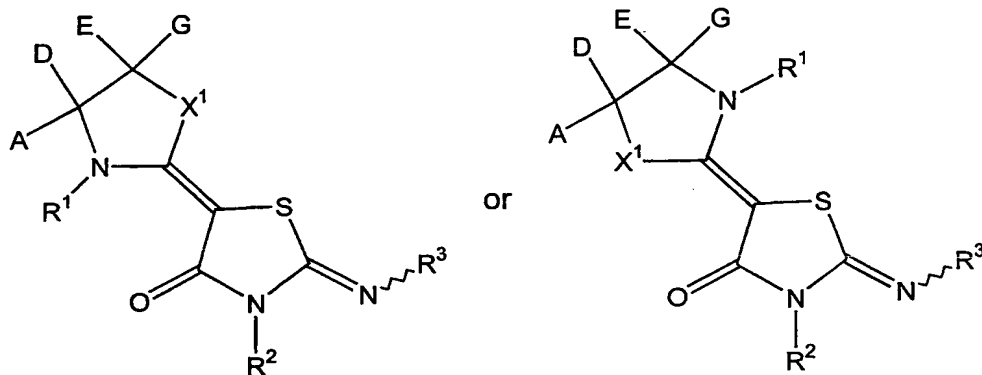
each Q<sup>1</sup> is independently unsubstituted or substituted with one or more substituents each independently selected from Q<sup>2</sup>;

- each Q<sup>2</sup> is independently halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxy carbonyl, aryloxy carbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylaryl aminoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylaryl amino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxy carbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxy carbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino,

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- heterocyclisulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyno, isothiocyano,
- 5 alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl,
- 10 alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two  $Q^2$  groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy, thioalkylenoxy or alkylenedithioxy where y is 1 or 2; or two  $Q^2$  groups, which substitute the same atom, together form alkylene;
- 15  $R^{50}$  is hydroxy, alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or  $-NR^{70}R^{71}$ , where  $R^{70}$  and  $R^{71}$  are each independently hydrogen, alkyl, aralkyl, aryl, heteroaryl, heteroaralkyl or heterocyclyl, or  $R^{70}$  and  $R^{71}$  together form alkylene, azaalkylene, oxaalkylene or thiaalkylene;
- $R^{51}$ ,  $R^{52}$  and  $R^{53}$  are each independently hydrogen, alkyl, aryl, aralkyl,
- 20 heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl;
- $R^{60}$  is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl; and
- $R^{63}$  is alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or  $-NR^{70}R^{71}$ .
2. The compound of claim 1, wherein  $X^1$  is S.
- 25 3. The compound of claim 1 or claim 2, wherein  $X^2$  is S.
4. The compound of any of claims 1-3, wherein  $X^3$  is O.
5. The compound of any of claims 1-4 that has formulae II:

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6. The compound of any of claims 1-5, wherein R<sup>1</sup> is unsubstituted alkyl.
7. The compound of any of claims 1-6, wherein R<sup>1</sup> is methyl.
- 5 8. The compound of any of claims 1-7, wherein R<sup>2</sup> is benzyl, phenyl, allyl, ethyl, butyl, cyclohexyl, propyl, 3-pyridylmethyl, 2-furylmethyl, 4-methoxycarbonylbzyl, 4-hydroxycarbonylbzyl, 2-phenethyl, 2-pyridylmethyl, 4-pyridylmethyl or 2-(4-morpholinyl)ethyl.
9. The compound of any of claims 1-8, wherein R<sup>2</sup> is benzyl, 3-pyridylmethyl or 2-furylmethyl.
- 10 10. The compound of any of claims 1-9, wherein R<sup>3</sup> is substituted or unsubstituted quinolyl, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted isoquinolyl, substituted or unsubstituted pyridyl, or substituted or unsubstituted indazolyl.
- 15 11. The compound of any of claims 1-10, wherein R<sup>3</sup> is substituted or unsubstituted phenyl.
12. The compound of any of claims 1-11, wherein R<sup>3</sup> is substituted with 0 to 5 substituents selected from ethylamino, cyano, cyclohexyl, hydroxy, methoxy, dimethylamino, amino, 4-morpholinyl, methylamino, isopropylamino, benzyloxy, methyl, isopropyl, nitro, trifluoromethyl, methylcarbonyl, chloro, propyl, ethoxy, methylcarbonylamino, aminocarbonyl, methoxycarbonyl, butylamino, benzylamino, cyclopentylamino, 1-pyrrolidinylamino, pyrrolidinyl, t-butylamino, 2,2,2-trifluoroethylamino, piperidinyl, trifluoromethoxy, hydroxycarbonyl, aminosulfonyl, methylcarbonylaminosulfonyl,
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trifluoromethylcarbonylamino and t-butoxycarbonyl, or any two substituents, which substitute atoms in a 1,2 arrangement, together form methylenedioxy.

13. The compound of any of claims 1-10 or 12, wherein R<sup>3</sup> is 5-quinolyl, 2-ethylamino-5-cyanophenyl, 4-cyclohexylphenyl, 2-hydroxy-1-naphthyl, 6-quinolyl, 3-methoxyphenyl, 4-dimethylaminophenyl, 4-aminophenyl, 4-(4-morpholinyl)phenyl, 2-methylamino-5-cyanophenyl, 2-dimethylamino-5-cyanophenyl, 2-ethylaminophenyl, 3-cyanophenyl, 2-aminophenyl, 2-isopropylamino-5-cyanophenyl, 4-benzyloxyphenyl, 2-methyl-4-hydroxy-5-isopropylphenyl, 2-ethylamino-5-nitrophenyl, 3-trifluoromethylphenyl, 3-methylcarbonylphenyl, 3-chlorophenyl, 2-propylphenyl, 2-ethoxyphenyl, 3-methylcarbonylaminophenyl, 3-aminocarbonylphenyl, 3-methoxycarbonylphenyl, 8-quinolyl, 8-hydroxy-5-quinolyl, 2-butylamino-5-cyanophenyl, 2-benzylamino-5-cyanophenyl, 2-cyclopentylamino-5-cyanophenyl, 2-(1-pyrrolidiny)amino-5-cyanophenyl, 5-isoquinolyl, 1-isoquinolyl, 4-methylcarbonylaminophenyl, 2-t-butylamino-5-cyanophenyl, 2-(2,2,2-trifluoroethyl)amino-5-cyanophenyl, 2-piperidinyl-5-cyanophenyl, 4-methylcarbonylphenyl, 4-aminocarbonylphenyl, 1-naphthyl, 2-naphthyl, 2-pyridyl, 3-pyridyl, 2-ethoxy-5-methylcarbonylaminophenyl, 4-pyridyl, 4-methoxycarbonylphenyl, 4-trifluoromethoxyphenyl, 5-indazolyl, 4-(imidazol-1-yl)phenyl, 3,4-methylenedioxyphenyl, 3-hydroxycarbonylphenyl, 2-ethylamino-5-methylcarbonylphenyl, 4-aminosulfonylphenyl, 4-methylcarbonylaminosulfonylphenyl, 3-methylcarbonylphenyl, 2-methylcarbonylamino-5-pyridyl, 4-cyano-3-methylcarbonylaminophenyl, 2-methylamino-5-methylcarbonylphenyl, 4-trifluoromethylcarbonylaminophenyl, 2-ethylamino-5-methoxycarbonylphenyl, 2-hydroxycarbonylphenyl or 2-ethylamino-5-t-butoxycarbonylphenyl.

14. The compound of any one of claims 1-13, wherein A and G are each independently selected from hydrogen, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted methyl and substituted or unsubstituted methylcarbonyl, or A and G together

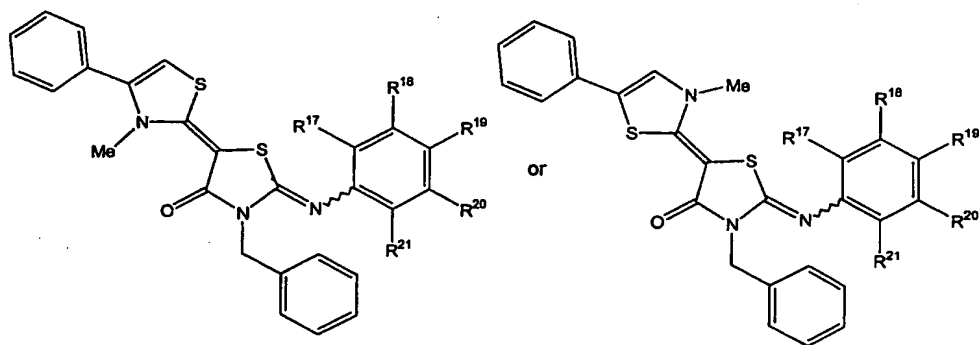


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from substituted or unsubstituted butylene, or substituted or unsubstituted propylene.

15. The compound of any one of claims 1-14, wherein A and G are each independently selected from hydrogen, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted methyl and substituted or unsubstituted methylcarbonyl, and are substituted with 0 to 4 substituents selected from chloro, bromo, methoxy, fluoro, ethoxy, nitro, trifluoromethyl, trifluoromethoxy, trifluoromethylcarbonylamino, dimethylaminocarbonyloxy, 2-(1-piperidinyl)ethoxy, 2-(1-methyl-4-piperazinyl)ethoxy, 2-(N-morpholinyl)ethoxy, 2-dimethylaminoethoxy, hydroxycarbonylmethoxy, methylcarbonylamino, hydroxy, ethylaminocarbonyloxy, methoxycarbonylmethoxy, aminocarbonylmethoxy, 2-hydroxyethoxy, 2-hydroxypropoxy, methyl, 2-chloroethylaminocarbonyloxy and 2-methylaminoethoxy.
16. The compound of any one of claims 1-15, wherein A and G are each independently selected from hydrogen, 4-nitrophenyl, 4-fluorophenyl, 4-chlorophenyl, 2-naphthyl, 4-bromophenyl, 2-methoxyphenyl, 3-fluorophenyl, 2,4-dimethoxyphenyl, 4-methylphenyl, 4-methoxyphenyl, methyl, phenyl and methylcarbonyl.
17. The compound of any one of claims 1-16, wherein D and E are each hydrogen or together form a bond.

18. The compound of any one of claims 1-17 that has formulae VI:

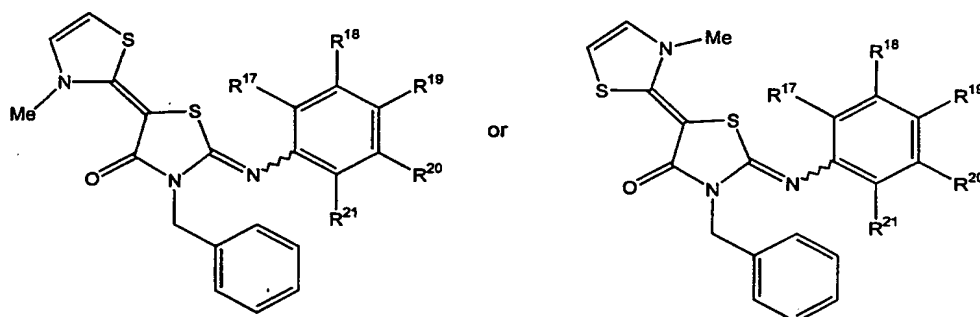


- or a pharmaceutically acceptable derivative thereof, wherein R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup> and R<sup>21</sup> are each independently selected from hydrogen, ethylamino, cyano,

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- cyclohexyl, hydroxy, methoxy, dimethylamino, amino, 4-morpholinyl, methylamino, isopropylamino, benzyloxy, methyl, isopropyl, nitro, trifluoromethyl, methylcarbonyl, chloro, propyl, ethoxy, methylcarbonylamino, aminocarbonyl, methoxycarbonyl, butylamino, benzylamino,
- 5 cyclopentylamino, 1-pyrrolidinylamino, pyrrolidinyl, t-butylamino, 2,2,2-trifluoroethylamino, piperidinyl, trifluoromethoxy, hydroxycarbonyl, aminosulfonyl, methylcarbonylaminosulfonyl, trifluoromethylcarbonylamino and t-butoxycarbonyl, or any two substituents, which substitute atoms in a 1,2 arrangement, together form methylenedioxy.

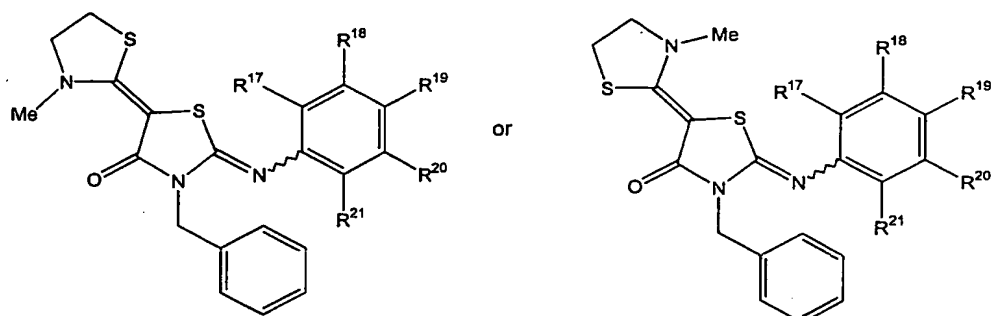
- 10 19. The compound of any of claims 1-17 that has formulae VII:



- or a pharmaceutically acceptable derivative thereof, wherein  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  are each independently selected from hydrogen, ethylamino, cyano, cyclohexyl, hydroxy, methoxy, dimethylamino, amino, 4-morpholinyl,
- 15 methylamino, isopropylamino, benzyloxy, methyl, isopropyl, nitro, trifluoromethyl, methylcarbonyl, chloro, propyl, ethoxy, methylcarbonylamino, aminocarbonyl, methoxycarbonyl, butylamino, benzylamino, cyclopentylamino, 1-pyrrolidinylamino, pyrrolidinyl, t-butylamino, 2,2,2-trifluoroethylamino, piperidinyl, trifluoromethoxy, hydroxycarbonyl,
- 20 aminosulfonyl, methylcarbonylaminosulfonyl, trifluoromethylcarbonylamino and t-butoxycarbonyl, or any two substituents, which substitute atoms in a 1,2 arrangement, together form methylenedioxy.

20. The compound of any of claims 1-17 that has formulae VIII:

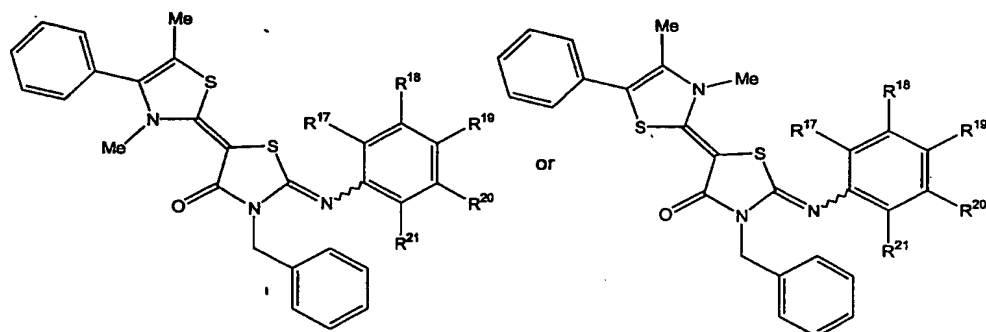
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or a pharmaceutically acceptable derivative thereof, wherein  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  are each independently selected from hydrogen, ethylamino, cyano, cyclohexyl, hydroxy, methoxy, dimethylamino, amino, 4-morpholinyl,

- 5 methylamino, isopropylamino, benzyloxy, methyl, isopropyl, nitro, trifluoromethyl, methylcarbonyl, chloro, propyl, ethoxy, methylcarbonylamino, aminocarbonyl, methoxycarbonyl, butylamino, benzylamino, cyclopentylamino, 1-pyrrolidinylamino, pyrrolidinyl, t-butylamino, 2,2,2-trifluoroethylamino, piperidinyl, trifluoromethoxy, hydroxycarbonyl,
- 10 aminosulfonyl, methylcarbonylaminosulfonyl, trifluoromethylcarbonylamino and t-butoxycarbonyl, or any two substituents, which substitute atoms in a 1,2 arrangement, together form methylenedioxy.

21. The compound of any of claims 1-17 that has formulae IX:



- 15 or a pharmaceutically acceptable derivative thereof, wherein  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  are each independently selected from hydrogen, ethylamino, cyano, cyclohexyl, hydroxy, methoxy, dimethylamino, amino, 4-morpholinyl, methylamino, isopropylamino, benzyloxy, methyl, isopropyl, nitro, trifluoromethyl, methylcarbonyl, chloro, propyl, ethoxy, methylcarbonylamino,

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aminocarbonyl, methoxycarbonyl, butylamino, benzylamino, cyclopentylamino, 1-pyrrolidinylamino, pyrrolidinyl, t-butylamino, 2,2,2-trifluoroethylamino, piperidinyl, trifluoromethoxy, hydroxycarbonyl, aminosulfonyl, methylcarbonylamino sulfonyl, trifluoromethylcarbonylamino and t-butoxycarbonyl, or any two substituents, which substitute atoms in a 1,2 arrangement, together form methylenedioxy.

22. The compound of any of claims 18-21, wherein  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  are each independently selected from (i) or (ii) as follows:

- (i)  $R^{21}$  is ethylamino;  $R^{18}$  is cyano; and  $R^{17}$ ,  $R^{19}$  and  $R^{20}$  are each hydrogen; or
- (ii)  $R^{17}$  is ethylamino;  $R^{20}$  is cyano; and  $R^{18}$ ,  $R^{19}$  and  $R^{21}$  are each hydrogen.

23. A compound selected from:

- 3-benzyl-2-(4-methoxyphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;
- 3-benzyl-2-(4-dimethylaminophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;
- 2-(4-aminophenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;
- 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(quinolin-6-ylimino)-thiazolidine-4-one;
- 2-(2-aminophenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;
- 3-benzyl-2-(4-benzyloxyphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;
- 3-benzyl-2-(2-hydroxy-1-naphthylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;
- 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile;
- 3-benzyl-2-(4-hydroxy-5-isopropyl-2-methylphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;

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- 3-benzyl-2-(2-ethylamino-5-nitrophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;  
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-[3-(trifluoromethyl)-phenylimino]thiazolidine-4-one;
- 5 2-(3-acetylphenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;  
3-benzyl-2-(3-chlorophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;  
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-propyl-
- 10 phenylimino)thiazolidine-4-one;  
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(quinolin-5-ylimino)-thiazolidine-4-one;  
3-benzyl-2-(2-ethoxyphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;
- 15 *N*-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}acetamide;  
3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzamide;  
3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-
- 20 ylideneamino]benzoic acid, methyl ester;  
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(pyridin-3-ylimino)-thiazolidine-4-one;  
*N*-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethoxyphenyl}acetamide;
- 25 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(pyridin-4-ylimino)-thiazolidine-4-one;  
4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzoic acid, methyl ester;  
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-[4-(trifluoro-
- 30 methoxy)phenylimino]thiazolidine-4-one;

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- 3-benzyl-2-(1*H*-indazol-5-ylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-thiazolidin-4-one;
- 3-benzyl-2-(4-imidazol-1-ylphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;
- 5 2-(benzo[1,3]dioxol-5-ylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;
- 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzoic acid;
- 3-benzyl-2-[2-(ethylamino)phenylimino]-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;
- 10 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(methylamino)benzonitrile;
- 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(isopropylamino)benzonitrile;
- 15 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(dimethylamino)benzonitrile;
- 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(*tert*-butylamino)benzonitrile;
- 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(2,2,2-trifluoroethylamino)benzonitrile;
- 20 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-piperidin-1-ylbenzonitrile;
- 2-[5-acetyl-2-(ethylamino)phenylimino]-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;
- 25 3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-morpholin-4-ylphenylimino)thiazolidin-4-one;
- 3-[3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(methylamino)benzonitrile;
- 4-dimethylamino-3-[3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile;
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- 3-[3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-yliden amino]-4-(isopropylamino)benzonitrile;  
3-[3-butyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile;
- 5 3-benzyl-5-(3-methyl-3*H*-benzoxazol-2-ylidene)-2-(quinolin-5-ylimino)-thiazolidin-4-one;  
*N*-[4-(3'-benzyl-3-methyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-[2,5']-bithiazolyliden-2'-ylideneamino)phenyl]acetamide;  
2'-[5-acetyl-2-(ethylamino)phenylimino]-3'-benzyl-3-methyl-4-phenyl-2',3'-
- 10 dihydro-3*H*-[2,5']bithiazolyliden-4'-one;  
3-(3'-benzyl-3-methyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-[2,5']bithiazol-yliden-2'-ylideneamino)-4-(ethylamino)benzonitrile;  
*N*-[4-(3'-benzyl-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)phenyl]acetamide;
- 15 *N*-[4-(3'-benzyl-3-methyl-4'-oxo-[2,5']bithiazolidinyliden-2'-ylidene-amino)phenyl]acetamide;  
3-(3'-benzyl-3,5-dimethyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-[2,5']-bithiazolyliden-2'-ylideneamino)-4-(ethylamino)benzonitrile;  
3-phenyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-benzylimino-thiazolidine-4-
- 20 one;  
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(8-quinolyl)imino-thiazolidine-4-one;  
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(8-hydroxy-5-quinolyl)imino-thiazolidine-4-one;
- 25 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(5-isoquinolyl)imino-thiazolidine-4-one;  
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(1-isoquinolyl)imino-thiazolidine-4-one;  
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-
- 30 methylcarbonylamino)phenylimino-thiazolidine-4-one;

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- 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-methylcarbonyl)phenylimino-thiazolidine-4-one;  
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-aminocarbonyl)phenylimino-thiazolidine-4-one;
- 5 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(1-naphthyl)imino-thiazolidine-4-one;  
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-naphthyl)imino-thiazolidine-4-one;  
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-pyridyl)imino-
- 10 thiazolidine-4-one;  
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-aminosulfonyl)phenylimino-thiazolidine-4-one;  
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-methylcarbonylamino-sulfonyl)phenylimino-thiazolidine-4-one;
- 15 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(3-methylcarbonyl)phenylimino-thiazolidine-4-one;  
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-methylcarbonylamino-5-pyridyl)imino-thiazolidine-4-one;  
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-cyano-3-
- 20 methylcarbonylamino-phenyl)imino-thiazolidine-4-one;  
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-ethylamino-5-methylcarbonylphenyl)imino-thiazolidine-4-one;  
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-methylamino-5-methylcarbonylphenyl)imino-thiazolidine-4-one;
- 25 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-trifluoromethyl-carbonylamino-phenyl)imino-thiazolidine-4-one;  
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-ethylamino-5-methoxycarbonylphenyl)imino-thiazolidine-4-one;  
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-
- 30 hydroxycarbonylphenyl)imino-thiazolidine-4-one;



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- 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-ethylamino-5-tert-butoxycarbonylphenyl)imino-thiazolidine-4-one;  
4-butylamino-3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 5 4-benzylamino-3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-cyclopentylamino-3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-pyrrolidinylamino-3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-
- 10 thiazolidin-2-ylideneamino]benzonitrile;  
4-pyrrolidinyl-3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-cyclohexyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 15 3-allyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-hydroxy-2-methyl-5-isopropylphenyl)imino-thiazolidine-4-one;  
3-cyclohexyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-hydroxy-1-naphthyl)imino-thiazolidine-4-one;  
4-ethylamino-3-[3-benzyl-5-(6-fluoro-3-methyl-3*H*-benzothiazol-2-ylidene)-4-
- 20 oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(6-ethoxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(6-nitro-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 25 4-ethylamino-3-[3-benzyl-5-(5-trifluoromethyl-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(6-methylcarbonylamino-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(5-hydroxy-3-methyl-3*H*-benzothiazol-2-ylidene)-
- 30 4-oxo-thiazolidin-2-ylideneamino]benzonitrile;

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- 4-ethylamino-3-[3-benzyl-5-(6-hydroxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(5-ethylaminocarbonyloxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
5 4-ethylamino-3-[3-benzyl-5-(5-methoxycarbonylmethoxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(5-aminocarbonylmethoxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(5-(2-hydroxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
10 4-ethylamino-3-[3-benzyl-5-(4-methoxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(4-methyl-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
15 4-ethylamino-3-[3-benzyl-5-(4-chloro-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(5-(2-chloroethylaminocarbonyloxy)-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(5-(2-methylaminoethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
20 4-ethylamino-3-[3-propyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
3-(3-pyridylmethyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(3-acetylphenyl)imino-thiazolidine-4-one;  
25 3-(3-pyridylmethyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-ethylamino-5-acetylphenyl)imino-thiazolidine-4-one;  
4-ethylamino-3-[3-(3-pyridylmethyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-(2-furylmethyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
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- 3-(4-methoxycarbonylbenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-ethylamino-5-acetylphenyl)imino-thiazolidine-4-one;  
3-(4-hydroxycarbonylbenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-ethylamino-5-acetylphenyl)imino-thiazolidine-4-one;
- 5 4-ethylamino-3-[3-(2-phenylethyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-(2-(4-morpholinyl)-1-ethyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
3-benzyl-5-(3-methylthiazolin-2-ylidene)-2-(4-
- 10 methylcarbonylaminophenyl)imino-thiazolidine-4-one;  
3-benzyl-5-(3-methyl-4-phenylthiazol-2-ylidene)-2-(4-methylcarbonylaminophenyl)imino-thiazolidine-4-one;  
3-benzyl-5-(3-methyl-4-phenylthiazol-2-ylidene)-2-(2-ethylamino-5-acetylphenyl)imino-thiazolidine-4-one;
- 15 3-benzyl-5-(3-methylthiazol-2-ylidene)-2-(4-methylcarbonylaminophenyl)imino-thiazolidine-4-one;  
4-ethylamino-3-[3-benzyl-5-(3-methyl-4-phenylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(3-methyl-4,5-dimethylthiazol-2-ylidene)-4-oxo-
- 20 thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(3-methyl-4-phenyl-5-methylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(3-methyl-4,5-butylenylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 25 4-ethylamino-3-[3-benzyl-5-(3-methyl-4-ethylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(3-methyl-4-(4-nitrophenyl)thiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(3-methyl-4-(4-fluorophenyl)thiazol-2-ylidene)-4-
- 30 oxo-thiazolidin-2-ylideneamino]benzonitrile;

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- 4-ethylamino-3-[3-benzyl-5-(3-methyl-4-(4-chlorophenyl)thiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(3-methyl-4-(4-methylphenyl)thiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 5 4-ethylamino-3-[3-benzyl-5-(3-methyl-4-(4-methoxyphenyl)thiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(3-methyl-4-methyl-5-acetylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(3-methyl-4,5-propylenylthiazol-2-ylidene)-4-oxo-
- 10 thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(3-methyl-4,5-diphenylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(3-methyl-4-methylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 15 4-ethylamino-3-[3-(3-pyridylmethyl)-5-(3-methyl-4,5-butylenylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile; and  
3-(4-methoxycarbonylbenzyl)-5-(3-methyl-4,5-butylenylthiazol-2-ylidene)-2-(2-ethylamino-5-acetylphenyl)imino-thiazolidine-4-one.
24. A compound selected from:
- 20 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(quinolin-8-ylimino)thiazolidin-4-one;  
3-benzyl-2-(8-hydroxyquinolin-5-ylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;  
3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-
- 25 ylideneamino]-4-butylaminobenzonitrile;  
4-benzylamino-3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile;  
3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-cyclopentylaminobenzonitrile;
- 30 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(pyrrolidin-1-ylamino)benzonitrile;

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- 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-pyrrolidin-1-ylbenzonitrile;  
3-benzyl-2-(isoquinolin-5-ylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;
- 5 3-benzyl-2-(isoquinolin-1-ylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;  
N-[4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl]acetamide;  
2-(4-acetylphenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;
- 10 4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzamide;  
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(naphthalen-1-ylimino)thiazolidin-4-one;
- 15 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(naphthalen-2-ylimino)thiazolidin-4-one;  
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(pyridin-2-ylimino)thiazolidin-4-one;  
4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzenesulfonamide;
- 20 N-acetyl-4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzenesulfonamide;  
2-(3-acetylphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-3-pyridin-3-ylmethylthiazolidin-4-one;
- 25 N-{5-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]pyridin-2-yl}acetamide;  
N-{5-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-2-cyanophenyl}acetamide;  
2-(5-acetyl-2-ethylaminophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-3-pyridin-3-ylmethylthiazolidin-4-one;
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- 4-ethylamino-3-[5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-3-pyridin-3-ylmethylthiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-furan-2-ylmethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile;
- 5 2-(5-acetyl-2-methylaminophenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;  
N-{4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-2,2,2-trifluoroacetamide;  
3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzoic acid methyl ester;
- 10 4-ethylamino-3-[5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-3-phenethylthiazolidin-2-ylideneamino]benzonitrile;  
2-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzoic acid;
- 15 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzoic acid *tert*-butyl ester;  
3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzoic acid;  
3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(2-hydroxyethylamino)benzonitrile;
- 20 {2-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-cyanophenylamino}acetic acid methyl ester;  
3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-N-ethyl-4-ethylaminobenzamide;
- 25 {2-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-cyanophenylamino}acetic acid;  
3-benzyl-2-(4-ethylaminopyridin-3-ylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;  
N-{4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-3-ethylaminophenyl}acetamide;
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- 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(2-dimethylaminoethylamino)benzonitrile;  
4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-*N*-ethyl-3-ethylaminobenzamide;
- 5 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-*N*-(2-dimethylaminoethyl)-4-ethylaminobenzamide;  
3-benzyl-2-[5-(4,5-dihydrooxazol-2-yl)-2-ethylamino-phenylimino]-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;  
3-[3-benzyl-5-(1-methyl-1*H*-quinolin-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;
- 10 2-(5-acetyl-2-ethylaminophenylimino)-3-benzyl-5-(1-methyl-1*H*-quinolin-2-ylidene)thiazolidin-4-one;  
3-benzyl-2-benzylimino-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;
- 15 2-(3-acetylphenylimino)-3-furan-2-ylmethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;  
*N*-{4-[3-furan-2-ylmethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}acetamide;  
[2-(5-acetyl-2-ethylaminophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-3-yl]acetic acid methyl ester;
- 20 *N*-{4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-2-cyanophenyl}acetamide;  
2-(5-acetyl-2-ethoxyphenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;
- 25 2-(5-acetyl-2-hydroxyphenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;  
2-(5-acetyl-2-ethylaminophenylimino)-3-benzyl-1-methyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)imidazolidin-4-one;  
4-ethylamino-3-[5-(3-methyl-3*H*-benzothiazol-2-ylidene)-3-(2-morpholin-4-ylethyl)-4-oxothiazolidin-2-ylideneamino]benzonitrile;
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- 4-ethylamino-3-[3-(4-methoxybenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-(3-methoxybenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile;
- 5 4-ethylamino-3-[3-(2-methoxybenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile;  
N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}succinamic acid;  
N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}benzenesulfonamide;
- 10 thiophene-2-sulfonic acid {3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}amide;  
N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-3-methoxybenzamide;
- 15 N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}methanesulfonamide;  
{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}carbamic acid ethyl ester;  
3-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-1,1-dimethylurea;
- 20 N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-2-morpholin-4-ylacetamide;  
N-{4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-2-morpholin-4-ylacetamide ;
- 25 N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-2-dimethylaminoacetamide;  
{4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}carbamic acid ethyl ester;  
N-{4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-2-dimethylaminoacetamide;
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- N-{4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}methanesulfonamide;  
4-ethylamino-3-[3-(3-hydroxybenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile;
- 5 4-ethylamino-3-[3-(3-fluorobenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile ;  
4-ethylamino-3-[3-(3-fluorobenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-3-(3-
- 10 trifluoromethylbenzyl)thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-3-(2-trifluoromethylbenzyl)thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[5-(3-methyl-3*H*-benzothiazol-2-ylidene)-3-(3-methylbenzyl)-4-oxothiazolidin-2-ylideneamino]benzonitrile;
- 15 N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl}-2-morpholin-4-ylacetamide;  
3-[3-(3-chlorobenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;  
3-[3-(3-bromobenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-
- 20 oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;  
N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl}-2,2,2-trifluoroacetamide;  
N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl}-2-dimethylaminoacetamide;
- 25 4-methylpiperazine-1-carboxylic acid {3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl}amide;  
2-(5-amino-2-ethylaminophenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;
- 30 N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl}-2-(4-methylpiperazin-1-yl)acetamide;

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- N-{3-[3-benzyl-5-(5-methoxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl}-2-dimethylaminoacetamide;
- N-{3-[3-benzyl-5-(5-hydroxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl}-2-dimethylaminoacetamide;
- 5 N-{3-[3-benzyl-5-[5-(2-chloroethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylamino-phenyl)-2-dimethylaminoacetamide;
- 10 N-(3-[3-benzyl-5-[5-(2-methoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylamino-phenyl)-2-dimethylaminoacetamide;
- N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl}-2-methoxyacetamide;
- 15 N-(3-[3-benzyl-5-[5-(2-dimethylaminoethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl)-2-dimethylaminoacetamide;
- N-(3-[3-benzyl-5-[5-(2-hydroxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl)-2-dimethylamino-
- 20 acetamide;
- 2-(5-acetyl-2-ethylaminophenylimino)-5-[5-(2-chloroethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-3-furan-2-ylmethylthiazolidin-4-one;
- 2-(5-acetyl-2-ethylaminophenylimino)-3-furan-2-ylmethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;
- 25 N-(3-[3-benzyl-5-[5-(2-chloroethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl)-2-methoxyacetamide;
- N-[4-ethylamino-3-[3-furan-2-ylmethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl]-2-methoxyacetamide;
- N-(3-[3-benzyl-5-[5-(2-dimethylaminoethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl)-2-
- 30 methoxyacetamide;

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- 2-(5-acetyl-2-ethylaminophenylimino)-5-[5-(2-dimethylamino-ethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-3-furan-2-ylmethylthiazolidin-4-one;  
N-(3-{5-[5-(2-dimethylaminoethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-3-furan-2-ylmethyl-4-oxothiazolidin-2-ylideneamino}-4-ethylaminophenyl)-2-methoxyacetamide;
- 5 acetic acid {3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenylcarbonyl}methyl ester;  
N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl}-2-hydroxyacetamide;
- 10 N-(3-{3-benzyl-5-[5-(2-methoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminophenyl)-2-hydroxyacetamide;  
2-(3-acetylphenylimino)-3-benzyl-5-[5-(2-methoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]thiazolidin-4-one;  
2-(5-acetyl-2-ethylaminophenylimino)-3-furan-2-ylmethyl-5-[5-(2-methoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]thiazolidin-4-one;
- 15 N-(4-ethylamino-3-{3-furan-2-ylmethyl-5-[5-(2-methoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}phenyl)-2-methoxyacetamide;  
2-(5-acetyl-2-ethylaminophenylimino)-3-benzyl-5-[5-(2-methoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]thiazolidin-4-one;
- 20 N-(3-{3-benzyl-5-[5-(2-methoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminophenyl)-2-methoxyacetamide;  
N-(3-{5-[5-(2-aminoethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-3-benzyl-4-oxothiazolidin-2-ylideneamino}-4-ethylaminophenyl)-2-dimethylaminoacetamide;
- 25 2-dimethylamino-N-{3-[3-furan-2-ylmethyl-5-(5-methoxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-phenyl}acetamide;  
3-(3'-benzyl-3,4,5-trimethyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile;
- 30 3-[3-benzyl-5-(3-methyl-4,5,6,7-tetrahydro-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;

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- 3-(3'-benzyl-4-ethyl-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile;
- 3-[3'-benzyl-3-methyl-4-(4-nitrophenyl)-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;
- 5 3-[3'-benzyl-4-(4-fluorophenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;
- 3-[3'-benzyl-4-(4-chloro-phenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;
- 3-(3'-benzyl-3-methyl-4'-oxo-4-p-tolyl-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile;
- 10 3-[3'-benzyl-4-(4-methoxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;
- 3-(5-acetyl-3'-benzyl-3,4-dimethyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile;
- 15 3-[3-benzyl-5-(3-methyl-3,4,5,6-tetrahydrocyclopentathiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;
- 3-(3'-benzyl-3-methyl-4'-oxo-4,5-diphenyl-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile;
- 3-(3'-benzyl-3,4-dimethyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile;
- 20 4-ethylamino-3-[5-(3-methyl-4,5,6,7-tetrahydro-3*H*-benzothiazol-2-ylidene)-4-oxo-3-pyridin-3-ylmethylthiazolidin-2-ylideneamino]benzonitrile;
- methyl 4-[2-(5-acetyl-2-ethylaminophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-3-ylmethyl]benzoate;
- 25 methyl 4-[2-(5-acetyl-2-ethylamino-phenylimino)-5-(3-methyl-4,5,6,7-tetrahydro-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-3-ylmethyl]benzoate;
- 4-[2-(5-acetyl-2-ethylaminophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-3-ylmethyl]benzoic acid;
- 3-[3-benzyl-5-(1-methyl-4,5,6,7-tetrahydro-1*H*-thiazolo[5,4-*c*]pyridin-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;
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- methyl 3-[2-(5-acetyl-2-ethylaminophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-3-ylmethyl]benzoate;  
3-[2-(5-acetyl-2-ethylaminophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-3-ylmethyl]benzoic acid;
- 5 2-(5-acetyl-2-ethylaminophenylimino)-3-benzyl-5-(3-methyl-4,5,6,7-tetrahydro-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;  
3-(3'-benzyl-4-biphenyl-4-yl-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile;  
3-(3'-benzyl-3-methyl-4-naphthalen-2-yl-4'-oxo-3',4'-dihydro-3*H*-
- 10 [2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile;  
3-[3'-benzyl-4-(4-bromophenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;  
3-[3'-benzyl-3-methyl-4-(2-nitrophenyl)-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;
- 15 2-(5-acetyl-2-ethylaminophenylimino)-5-(3-methyl-4,5,6,7-tetrahydro-3*H*-benzothiazol-2-ylidene)-3-pyridin-3-ylmethylthiazolidin-4-one;  
3-[3'-benzyl-4-(2-methoxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;  
3-[3'-benzyl-4-(3-fluorophenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-
- 20 [2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;  
3-[3'-benzyl-3-methyl-4'-oxo-4-(4-trifluoromethylphenyl)-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;  
3-[3'-benzyl-3-methyl-4'-oxo-4-(4-trifluoromethoxyphenyl)-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;
- 25 3-[3'-benzyl-4-(2,4-dimethoxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;  
3-(3'-benzyl-5-ethyl-3-methyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile;  
3-[3'-benzyl-3-methyl-4'-oxo-4-(2-trifluoromethylphenyl)-3',4'-dihydro-3*H*-
- 30 [2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;

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- 3-[3'-benzyl-4-(3-bromophenyl)-3,5-dimethyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;  
3-[3'-benzyl-4-(3-methoxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;
- 5 3-benzyl-2-[4-(1,1,1,3,3,3-hexafluoro-2-hydroxyisopropyl)-phenylimino]-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;  
3-(3'-benzyl-4-chloromethyl-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile;  
3'-benzyl-2'-(5-cyano-2-ethylaminophenylimino)-3-methyl-4'-oxo-3',4'-dihydro-
- 10 3*H*,2'*H*-[2,5']bithiazolylidene-4-carboxylic acid ethyl ester;  
3-(4,3'-dibenzyl-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile;  
3'-benzyl-2'-(5-cyano-2-ethylaminophenylimino)-3-methyl-4'-oxo-3',4'-dihydro-3*H*,2'*H*-[2,5']bithiazolylidene-4-carboxylic acid;
- 15 3-benzyl-2-[2-ethylamino-5-(1-hydroxyethyl)phenylimino]-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;  
3-[3'-benzyl-4-(2-hydroxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;  
3-benzyl-2-[2-ethylamino-5-(1-hydroxyiminoethyl)phenylimino]-5-(3-methyl-
- 20 3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;  
3-benzyl-2-[2-ethylamino-5-(1-methoxyiminoethyl)phenylimino]-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;  
3-benzyl-2-[5-(1-benzyloxyiminoethyl)-2-ethylaminophenylimino]-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;
- 25 3-benzyl-2-[2-ethylamino-5-[1-(phenylhydrazono)ethyl]-phenylimino]-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;  
3-(4,3'-dibenzyl-3,5-dimethyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile;  
3-[3-cyclohexylmethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-
- 30 oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;

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- 3-[3'-benzyl-4-(3-hydroxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-yliden amino]-4-ethylaminobenzonitrile;  
3-[3'-benzyl-4-(4-hydroxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;
- 5 3-(3'-benzyl-3,4-dimethyl-4'-oxo-5-phenyl-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile;  
2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-3,5-dimethyl-4-phenyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one;  
2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-3,4-dimethyl-5-phenyl-2',3'-
- 10 dihydro-3*H*-[2,5']bithiazolyliden-4'-one;  
2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-4-(4-methoxyphenyl)-3,5-dimethyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one;  
2'-(5-acetyl-2-ethylaminophenylimino)-4,3'-dibenzyl-3-methyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one;
- 15 2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-4-(2-methoxyphenyl)-3,5-dimethyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one;  
3-{3-benzyl-5-[5-(2-dimethylaminoacetyl)-1-methyl-4,5,6,7-tetrahydro-1*H*-thiazolo[5,4-*c*]pyridin-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile;
- 20 2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-4-(3-methoxyphenyl)-3,5-dimethyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one;  
2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-4-(3-hydroxyphenyl)-3,5-dimethyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one;  
2'-(5-acetyl-2-ethylaminophenylimino)-3,3'-dibenzyl-5-methyl-4-phenyl-2',3'-
- 25 dihydro-3*H*-[2,5']bithiazolyliden-4'-one;  
N-(3-{3-benzyl-5-[5-(2-acetoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminophenyl)-2-dimethylaminoacetamide;
- 30 2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-3-(2-methoxyethyl)-5-methyl-4-phenyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one;

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- 2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-3-(3-methoxypropyl)-5-methyl-4-phenyl-2',3'-dihydro-3*H*-[2,5]bithiazolyliden-4'-one;  
[2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-5-methyl-4'-oxo-4-phenyl-3',4'-dihydro-2'*H*-[2,5]bithiazolyliden-3-yl]acetic acid methyl ester;
- 5 [2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-5-methyl-4'-oxo-4-phenyl-3',4'-dihydro-2'*H*-[2,5]bithiazolyliden-3-yl]acetic acid;  
2-[2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-5-methyl-4'-oxo-4-phenyl-3',4'-dihydro-2'*H*-[2,5]bithiazolyliden-3-yl]ethyl acetate;  
2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-3-(2-hydroxyethyl)-5-methyl-
- 10 4-phenyl-2',3'-dihydro-3*H*-[2,5]bithiazolyliden-4'-one;  
N-[3-(3'-benzyl-3,5-dimethyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-[2,5]bithiazolyliden-2'-ylideneamino)-4-ethylaminophenyl]-2-methoxyacetamide;  
N-[3-(3'-benzyl-3,5-dimethyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-
- 15 [2,5]bithiazolyliden-2'-ylideneamino)-4-ethylaminophenyl]-2-dimethylaminoacetamide;  
3-[3-cyclohexyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;  
3-[3-allyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-
- 20 ylideneamino]-4-ethylaminobenzonitrile;  
3-allyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(quinolin-5-ylimino)thiazolidin-4-one;  
3-allyl-2-(4-hydroxy-5-isopropyl-2-methylphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;
- 25 4-ethylamino-3-[5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-3-phenylthiazolidin-2-ylideneamino]benzonitrile;  
3-cyclohexyl-2-(2-hydroxynaphthalen-1-ylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;  
3-allyl-2-(2-hydroxynaphthalen-1-ylimino)-5-(3-methyl-3*H*-benzothiazol-2-
- 30 ylidene)thiazolidin-4-one;



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- 2-(4-cyclohexylphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-3-phenylthiazolidin-4-one;
- 3-[3-benzyl-5-(6-fluoro-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;
- 5 3-[3-benzyl-5-(5-chloro-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;
- 3-[3-benzyl-5-(6-ethoxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;
- 4-ethylamino-3-[5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-3-propylthiazolidin-2-ylideneamino]benzonitrile;
- 10 3-[3-benzyl-5-(3-methyl-6-nitro-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;
- N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}acetamide;
- 15 3-[3-benzyl-5-(6-hydroxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;
- ethylcarbamic acid 2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yl ester;
- {2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yloxy}acetic acid methyl ester;
- 20 3-methyl-2,3-dihydrobenzothiazol-5-yloxy}acetic acid methyl ester;
- 2-[2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yloxy}acetamide;
- (2-chloroethyl)carbamic acid 2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yl ester;
- 25 3-[3-benzyl-5-[3-methyl-5-(2-methylaminoethoxy)-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;
- 3-[3-benzyl-5-[5-(3-hydroxypropoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;

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- (3-chloropropyl)carbamic acid 2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yl ester;
- 3-(3-benzyl-5-[3-methyl-5-[2-(4-methylpiperazin-1-yl)-ethoxy]-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino)-4-ethylaminobenzonitrile;
- 5 3-[3-benzyl-5-[3-methyl-5-(2-piperidin-4-ylethoxy)-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;
- 3-[3-benzyl-5-[5-(2-dimethylaminoethoxy)-3-methyl-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;
- 10 {2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yloxy}acetic acid;
- 3-[3-benzyl-5-[6-(2-hydroxyethoxy)-3-methyl-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;
- 15 3-[3-benzyl-5-[6-(2-methoxyethoxy)-3-methyl-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;
- 3-[3-benzyl-5-[3-methyl-6-(2-morpholin-4-ylethoxy)-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;
- 3-[3-benzyl-5-[5-(2-methoxyethoxy)-3-methyl-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;
- 20 3-[3-benzyl-5-[3-methyl-4-methoxy-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;
- 3-[3-benzyl-5-[3-methyl-4-methyl-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;
- 25 3-[3-benzyl-5-[3-methyl-4-chloro-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;
- 3-[3-benzyl-5-[3-methyl-6-trifluoromethoxy-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;
- 3-[3-benzyl-5-(3,5,6-trimethyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;
- 30

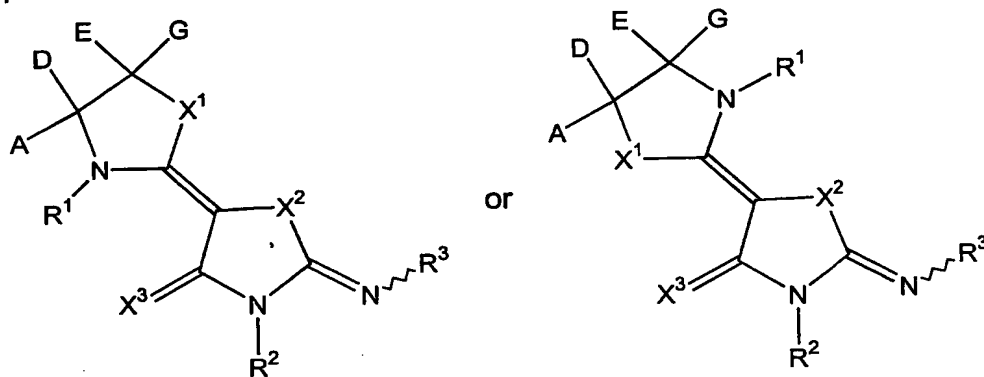
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- 3-[3-benzyl-5-(3-methyl-5-acetamido-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;  
N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazilidin-6-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yl}-2,2,2-trifluoroacetamide;
- 5 3-[5-(6-amino-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;  
N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}-N',N''-di(tert-butoxycarbonyl)guanidine;
- 10 2-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazilidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}-1,1,-dimethylurea;  
N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazilidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yl}-2,2,2-trifluoroacetamide;  
3-[5-(5-amino-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;
- 15 {2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazilidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}carbamic acid ethyl ester;  
N-[2-(3-benzyl-2-{5-cyano-2-[ethyl-(2-morpholin-ylethyl)amino]phenylimino}-4-oxothiazilidin-5-ylidene)-3-methyl-2,3-dihydrobenzothiazol-6-yl]-2,2,2-trifluoroacetamide;
- 20 N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazilidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}-2,2,2-trifluoro-N-(2-morpholin-4ylethyl)acetamide;  
3-[3-benzyl-5-[3-methyl-6-(2-morpholin-4-yl-ethylamino)-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;
- 25 3-[3-benzyl-5-[3-methyl-6-(2-piperidin-1-yl-ethylamino)-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;  
N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazilidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yl}-2,2,2-trifluoro-N-(2-morpholin-4ylethyl)acetamide;
- 30

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- 3-{3-benzyl-5-[3-methyl-5-(2-morpholin-4-yl-ethylamino)-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile;  
 N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}guanidine;
- 5 3-{3-benzyl-5-[3-methyl-6-(4-trifluoromethylbenzylamino)-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile;  
 N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}-N-(3-fluoropropyl)-2,2,2-trifluoroacetamide;
- 10 N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}-N-(3-cyanopropyl)-2,2,2-trifluoroacetamide;  
 3-{3-benzyl-5-[6-(3-cyanopropylamino)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-(ethylamino)benzonitrile;
- 15 3-{3-benzyl-5-[6-(3-hydroxypropylamino)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-(ethylamino)benzonitrile; and  
 3-{3-benzyl-5-[6-(2-methoxyethylamino)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-(ethylamino)benzonitrile.

25. A pharmaceutical composition, comprising, in a  
 20 pharmaceutically acceptable carrier, a compound formulae I:



or a pharmaceutically acceptable derivative thereof, wherein:

A, D, E and G are selected from (i) or (ii) as follows:

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(i) A and G are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroarylum, substituted or unsubstituted heteroarylumalkyl, halo, pseudohalo,  $OR^{10}$ ,  $SR^{10}$ ,  $S(=O)R^{13}$ ,  $S(=O)_2R^{13}$ ,  $NR^{11}R^{12}$  and  $C(=J)R^{13}$ , or A and G together form substituted or unsubstituted alkylene, substituted or unsubstituted azaalkylene, substituted or unsubstituted oxaalkylene, substituted or unsubstituted thiaalkylene, substituted or unsubstituted alkenylene, substituted or unsubstituted alkynylene, substituted or unsubstituted 1,3-butadienylene, substituted or unsubstituted 1-aza-1,3-butadienylene, or substituted or unsubstituted 2-aza-1,3-butadienylene;

D and E are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo and pseudohalo or D and E together form a bond; or

(ii) A and D; or E and G; together form substituted or unsubstituted alkylene, substituted or unsubstituted azaalkylene, substituted or unsubstituted oxaalkylene, or substituted or unsubstituted thiaalkylene; and the others of A, D, E and G are selected as in (i);

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$X^1$  and  $X^2$  are each independently selected from O, S, S(=O), S(=O)<sub>2</sub>, Se, NR<sup>5</sup>, CR<sup>6</sup>R<sup>7</sup> and CR<sup>8</sup>=CR<sup>9</sup>;

$X^3$  is O, S, Se, NR<sup>5</sup> or CR<sup>6</sup>R<sup>7</sup>;

$R^1$  and  $R^2$  are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroarylium, substituted or unsubstituted heteroaryliumalkyl, OR<sup>10</sup>, SR<sup>10</sup>, S(=O)R<sup>13</sup>, S(=O)<sub>2</sub>R<sup>13</sup>, NR<sup>11</sup>R<sup>12</sup> and C(=J)R<sup>13</sup>;

$R^3$  is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylium, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroaryliumalkyl, OR<sup>10</sup>, SR<sup>10</sup>, S(=O)R<sup>13</sup>, S(=O)<sub>2</sub>R<sup>13</sup>, NR<sup>11</sup>R<sup>12</sup> and C(=J)R<sup>13</sup>; where

$R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$  and  $R^9$  are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo, pseudohalo, OR<sup>10</sup>, NR<sup>14</sup>R<sup>15</sup> and C(=J)R<sup>13</sup>;

$R^{10}$ ,  $R^{11}$  and  $R^{12}$  are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or

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- unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted
- 5 aralkyl, substituted or unsubstituted heteroaralkyl or  $C(=J)R^{13}$ ;  
 J is O, S or  $NR^{14}$ ;  
 $R^{13}$  is selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
- 10 heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, pseudohalo,  $OR^{16}$  and  $NR^{14}R^{15}$ ;  
 $R^{14}$ ,  $R^{15}$  and  $R^{16}$  are each independently selected from hydrogen, alkyl,
- 15 alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl;  
 where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclalkyl, aryl, heteroaryl, heteroarylum, aralkyl, heteroaralkyl and heteroarylumalkyl moieties of A, D, E, G,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^5$ ,  $R^6$ ,
- 20  $R^7$ ,  $R^8$ ,  $R^9$ ,  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$  and  $R^{13}$  are unsubstituted or substituted with one or more substituents each independently selected from  $Q^1$ , where  $Q^1$  is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl
- 25 containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxy carbonyl, aryloxy carbonylalkyl, aralkoxycarbonyl,
- 30 aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl,

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- arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, aralkoxycarbonyloxy,
- 5 aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido,
- 10 N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, imino, hydroxyimino, alkoxyimino, aryloxyimino, aralkoxyimino, alkylazo, arylazo, aralkylazo, aminothiocabonyl, alkylaminothiocabonyl, arylaminothiocabonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl,
- 15 arylaminoalkyl, diarylaminoalkyl, alkylarylaminominoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylaminomino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino,
- 20 heteroarylsulfonylamino, heterocyclisulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy,
- 25 alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl,
- 30 dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two Q<sup>1</sup> groups, which substitute atoms in a 1,2 or



**5** substituents each independently selected from  $Q^2$ ;

**10** cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkylidiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxy carbonyl, aryloxy carbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl,

**15** arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy,

**20** aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-

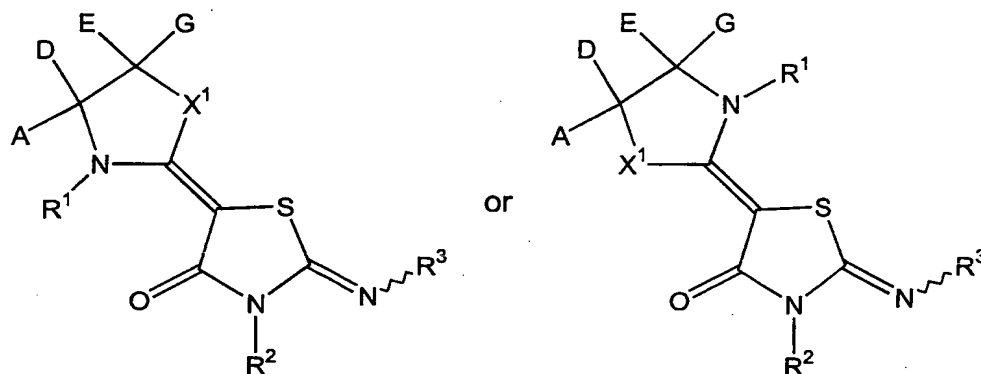
**25** diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl,

**30** alkylarylaminooalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino,

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- aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclisulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy,
- 10 alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two  $Q^2$  groups, which
- 15 substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy, thioalkylenoxy or alkylenedithioxy where y is 1 or 2; or two  $Q^2$  groups, which substitute the same atom, together form alkylene;
- each  $Q^2$  is independently unsubstituted or substituted with one or more substituents each independently selected from alkyl, halo and pseudohalo;
- 20  $R^{50}$  is hydroxy, alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or  $-NR^{70}R^{71}$ , where  $R^{70}$  and  $R^{71}$  are each independently hydrogen, alkyl, aralkyl, aryl, heteroaryl, heteroaralkyl or heterocyclyl, or  $R^{70}$  and  $R^{71}$  together form alkylene, azaalkylene, oxaalkylene or thiaalkylene;
- $R^{51}$ ,  $R^{52}$  and  $R^{53}$  are each independently hydrogen, alkyl, aryl, aralkyl,
- 25 heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl;
- $R^{60}$  is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl; and
- $R^{63}$  is alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or  $-NR^{70}R^{71}$ .
26. The pharmaceutical composition of claim 25, wherein the
- 30 compound has formulae II:

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or a pharmaceutically acceptable derivative thereof, wherein:

A, D, E and G are selected from (i) or (ii) as follows:

- (i) A and G are each independently selected from hydrogen,  
 5 substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl,  
 substituted or unsubstituted alkynyl, substituted or unsubstituted  
 cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or  
 unsubstituted cycloalkylalkyl, substituted or unsubstituted  
 heterocyclalkyl, substituted or unsubstituted aryl, substituted or  
 10 unsubstituted heteroaryl, substituted or unsubstituted aralkyl,  
 substituted or unsubstituted heteroaralkyl, substituted or unsubstituted  
 heteroarylium, substituted or unsubstituted heteroaryliumalkyl, halo,  
 pseudohalo, OR<sup>10</sup>, SR<sup>10</sup>, S(=O)R<sup>13</sup>, S(=O)<sub>2</sub>R<sup>13</sup>, NR<sup>11</sup>R<sup>12</sup> and C(=J)R<sup>13</sup>,  
 or A and G together form substituted or unsubstituted alkylene,  
 15 substituted or unsubstituted azaalkylene, substituted or unsubstituted  
 oxaalkylene, substituted or unsubstituted thiaalkylene, substituted or  
 unsubstituted alkenylene, substituted or unsubstituted alkynylene,  
 substituted or unsubstituted 1,3-butadienylene, substituted or  
 unsubstituted 1-aza-1,3-butadienylene, or substituted or unsubstituted  
 20 2-aza-1,3-butadienylene;

D and E are each independently selected from hydrogen,  
 substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl,  
 substituted or unsubstituted alkynyl, substituted or unsubstituted  
 cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or

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- unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo and pseudohalo or D and E together form a bond; or
- (ii) A and D; or E and G; together form substituted or unsubstituted alkylene, substituted or unsubstituted azaalkylene, substituted or unsubstituted oxaalkylene, or substituted or unsubstituted thiaalkylene; and the others of A, D, E and G are selected as in (i);
- $X^1$  is selected from O, S, Se,  $NR^5$ ,  $CR^6R^7$  and  $CR^8=CR^9$ ;
- $R^1$  and  $R^2$  are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroarylium, substituted or unsubstituted heteroaryliumalkyl,  $OR^{10}$ ,  $SR^{10}$ ,  $S(=O)R^{13}$ ,  $S(=O)_2R^{13}$ ,  $NR^{11}R^{12}$  and  $C(=J)R^{13}$ ;
- $R^3$  is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylium, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroaryliumalkyl,  $OR^{10}$ ,  $SR^{10}$ ,  $S(=O)R^{13}$ ,  $S(=O)_2R^{13}$ ,  $NR^{11}R^{12}$  and  $C(=J)R^{13}$ ;
- where:
- $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$  and  $R^9$  are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl,

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- substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo,
- 5 pseudohalo, OR<sup>10</sup>, NR<sup>14</sup>R<sup>15</sup> and C(=J)R<sup>13</sup>;
- R<sup>10</sup>, R<sup>11</sup> and R<sup>12</sup> are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl,
- 10 substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl or C(=J)R<sup>13</sup>;
- J is O, S or NR<sup>14</sup>;
- R<sup>13</sup> is selected from hydrogen, substituted or unsubstituted alkyl,
- 15 substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or
- 20 unsubstituted heteroaralkyl, pseudohalo, OR<sup>16</sup> and NR<sup>14</sup>R<sup>15</sup>;
- R<sup>14</sup>, R<sup>15</sup> and R<sup>16</sup> are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl;
- where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl,
- 25 cycloalkylalkyl, heterocyclalkyl, aryl, heteroaryl, heteroarylium, aralkyl, heteroaralkyl and heteroaryliumalkyl moieties of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup> and R<sup>13</sup> are unsubstituted or substituted with one or more substituents each independently selected from Q<sup>1</sup>, where Q<sup>1</sup> is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto,
- 30 hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl

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- containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkylidiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl,
- 5 alkoxycarbonylalkyl, aryloxy carbonyl, aryloxy carbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy,
- 10 aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-
- 15 N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, aminothiocabonyl, alkylaminothiocabonyl,
- 20 arylaminothiocabonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylaminalkyl, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxy carbonylaminoalkyl, aryloxyarylcarbonylamino,
- 25 aryloxy carbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio,
- 30 hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy,

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- alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylamino sulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl,
- 5 dialkylaminosulfonyl, arylaminosulfonyl, diarylamino sulfonyl or alkylarylaminosulfonyl; or two Q<sup>1</sup> groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy, thioalkylenoxy or alkylenedithioxy; or two Q<sup>1</sup> groups, which substitute the same atom, together form alkylene;
- 10 each Q<sup>1</sup> is independently unsubstituted or substituted with one or more substituents each independently selected from Q<sup>2</sup>;
- each Q<sup>2</sup> is independently halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2
- 15 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkylidiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxy carbonyl,
- 20 aryloxy carbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylamino carbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy,
- 25 arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylamino carbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido,
- 30 N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-

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- diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl,
- 5 alkylarylaminooalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino,
- 10 heterocyclisulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy,
- 15 hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl,
- 20 diarylaminosulfonyl or alkylarylaminosulfonyl; or two  $Q^2$  groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy (*i.e.*,  $-O-(CH_2)_y-O-$ ), thioalkylenoxy (*i.e.*,  $-S-(CH_2)_y-O-$ ) or alkylenedithioxy (*i.e.*,  $-S-(CH_2)_y-S-$ ) where y is 1 or 2; or two  $Q^2$  groups, which substitute the same atom, together form alkylene;
- 25  $R^{50}$  is hydroxy, alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or  $-NR^{70}R^{71}$ , where  $R^{70}$  and  $R^{71}$  are each independently hydrogen, alkyl, aralkyl, aryl, heteroaryl, heteroaralkyl or heterocyclyl, or  $R^{70}$  and  $R^{71}$  together form alkylene, azaalkylene, oxaalkylene or thiaalkylene;
- $R^{51}$ ,  $R^{52}$  and  $R^{53}$  are each independently hydrogen, alkyl, aryl, aralkyl,
- 30 heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl;



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$R^{60}$  is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclalkyl; and

$R^{63}$  is alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or  $-NR^{70}R^{71}$ .

27. The pharmaceutical composition of claim 25 or claim 26,  
 5 wherein A and G are each independently selected from hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted aryl, or together form substituted or unsubstituted 1,3-butadienyl.

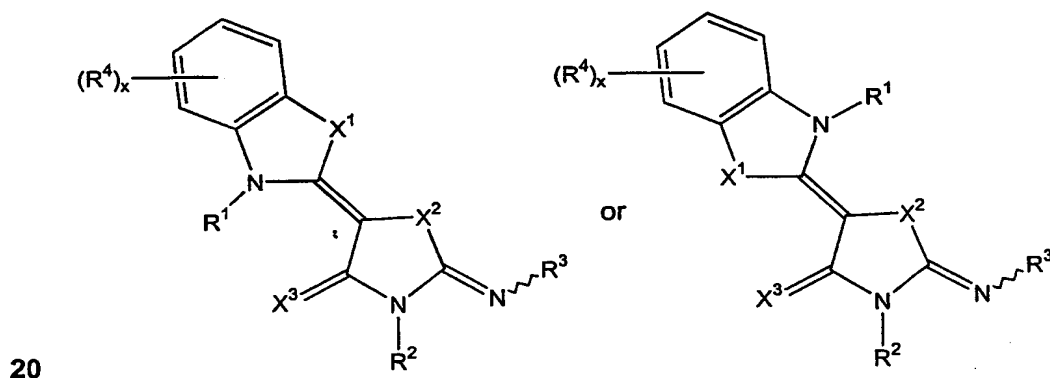
28. The pharmaceutical composition of any of claims 25-27, wherein  
 A and G are each independently hydrogen, methyl or phenyl, or together form  
 10 substituted or unsubstituted 1,3-butadienyl.

29. The pharmaceutical composition of any of claims 25-28, wherein  
 A and G are both hydrogen.

30. The pharmaceutical composition of any of claims 25-29, wherein  
 D and E are each hydrogen, or together form a bond.

- 15 31. The pharmaceutical composition of any of claims 25-30, wherein  
 D and E together form a bond, and A and G together form substituted or unsubstituted 1,3-butadienyl.

32. The pharmaceutical composition of claim 25, wherein the  
 compound has formulae III:



or a pharmaceutically acceptable derivative thereof, wherein:

each  $R^4$  is independently substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted

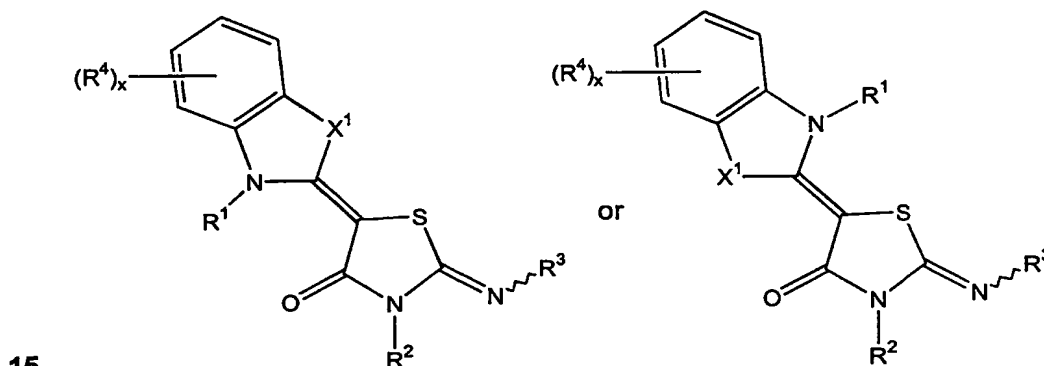
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- or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted guanidino, substituted or unsubstituted
- 5 isothioureido, halo, pseudohalo,  $\text{OR}^{10}$ ,  $\text{SR}^{10}$ ,  $\text{S(=O)R}^{13}$ ,  $\text{S(=O)}_2\text{R}^{13}$ ,  $\text{NR}^{11}\text{R}^{12}$  or  $\text{C(=J)R}^{13}$ ;

x is an integer from 0 to 4; and

- the amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclalkyl, cycloalkylalkyl, heterocyclalkyl, aryl, heteroaryl, heteroarylium, aralkyl, heteroaralkyl and heteroaryliumalkyl moieties of  $\text{R}^4$  are unsubstituted or
- 10 substituted with one or more substituents each independently selected from  $\text{Q}^2$ .

33. The pharmaceutical composition of claim 32, wherein the compound has formulae IV:



or a pharmaceutically acceptable derivative thereof, wherein:

- each  $\text{R}^4$  is independently substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted guanidino, substituted or unsubstituted
- 20

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isothioureido, halo, pseudohalo,  $OR^{10}$ ,  $SR^{10}$ ,  $S(=O)R^{13}$ ,  $S(=O)_2R^{13}$ ,  $NR^{11}R^{12}$  or  $C(=J)R^{13}$ ;

x is an integer from 0 to 4; and

the amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl,

- 5 cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, heteroarylium, aralkyl, heteroaralkyl and heteroaryliumalkyl moieties of  $R^4$  are unsubstituted or substituted with one or more substituents each independently selected from  $Q^2$ .

34. The pharmaceutical composition of any of claims 25-33, wherein  
10  $X^1$  is O, S or  $NR^5$ .

35. The pharmaceutical composition of any of claims 25-34, wherein  $X^1$  is O or S.

36. The pharmaceutical composition of any of claims 25-35, wherein  $X^1$  is S.

- 15 37. The pharmaceutical composition of any of claims 25-36, wherein  $R^1$  is substituted or unsubstituted alkyl.

38. The pharmaceutical composition of any of claims 25-37, wherein  $R^1$  is methyl.

39. The pharmaceutical composition of any of claims 25-38, wherein  
20  $R^2$  is substituted or unsubstituted alkyl or substituted or unsubstituted aralkyl.

40. The pharmaceutical composition of any of claims 25-39, wherein  $R^2$  is ethyl, n-butyl or benzyl.

41. The pharmaceutical composition of any of claims 25-40, wherein  $R^2$  is benzyl.

- 25 42. The pharmaceutical composition of any of claims 25-41, wherein  $R^3$  is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

43. The pharmaceutical composition of any of claims 25-42, wherein  $R^3$  is substituted or unsubstituted phenyl, substituted or unsubstituted  
30 naphthyl, substituted or unsubstituted pyridyl, substituted or unsubstituted indazolyl, or substituted or unsubstituted quinolynyl. In certain embodiments,

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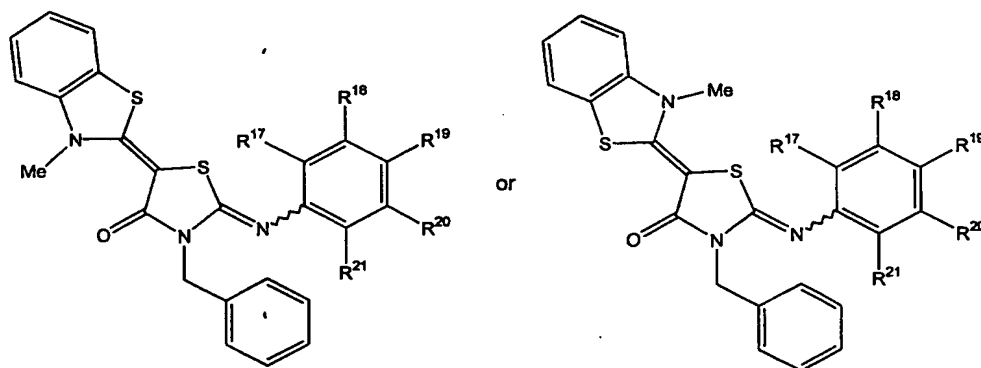
R<sup>3</sup> is substituted or unsubstituted phenyl or substituted or unsubstituted naphthyl.

44. The pharmaceutical composition of any of claims 25-43, wherein R<sup>3</sup> is substituted or unsubstituted phenyl.

- 5 45. The pharmaceutical composition of any of claims 25-44, wherein Q<sup>1</sup> is selected from halo, hydroxy, nitrile, nitro, hydroxycarbonyl, alkyl, haloalkyl, polyhaloalkyl, heteroaryl, alkylcarbonyl, alkoxy, aminocarbonyl, alkoxy, perfluoroalkoxy, aralkoxy, amino, alkylamino, dialkylamino, haloalkylamino, alkylcarbonylamino, dialkylcarbonyloxy or  
 10 heterocyclyl; or two Q<sup>1</sup> groups, which substitute atoms in a 1,2 arrangement, form alkylenedioxy.

46. The pharmaceutical composition of any of claims 25-45, wherein Q<sup>1</sup> is methoxy, dimethylamino, NH<sub>2</sub>, benzyloxy, hydroxy, CN, isopropyl, methyl, nitro, ethylamino, trifluoromethyl, acetyl, chloro, n-propyl, ethoxy,  
 15 methylcarbonylamino, CONH<sub>2</sub>, methoxycarbonyl, methylamino, trifluoromethoxy, imidazolyl, hydroxycarbonyl, isopropylamino, tert-butylamino, 2,2,2-trifluoroethylamino, piperidinyl, dimethylaminocarbonyloxy, 2-hydroxyethoxy, 2-(N-morpholinyl)ethoxy or morpholinyl, or two Q<sup>1</sup> groups, which substitute atoms in a 1,2 arrangement, form methylenedioxy.

- 20 47. The pharmaceutical composition of any of claims 25-46, wherein the compound has formulae V:



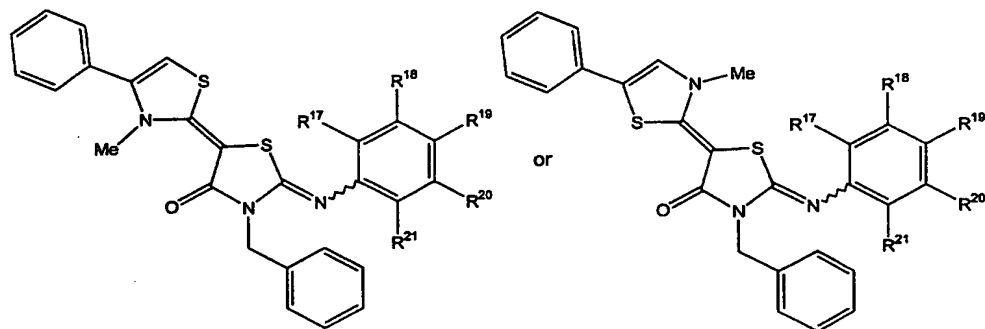
or a pharmaceutically acceptable derivative thereof, wherein:

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- $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  are each independently selected from hydrogen, halo, pseudohalo, hydroxyl, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl
- 5 containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxy carbonyl, aryloxy carbonylalkyl, aralkoxycarbonyl,
- 10 aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy,
- 15 alkoxycarbonyloxy, aryloxy carbonyloxy, aralkoxycarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-
- 20 aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino,
- 25 diarylamino, alkylaryl amino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxy carbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxy carbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroaryl/sulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,
- 30  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio,

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- perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, 5 diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl, or any two of  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$ , which substitute adjacent carbons on the ring, together form
- 10 alkylenedioxy; and
- the aryl and heteroaryl groups of  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  are unsubstituted or substituted with one or more substituents each independently selected from  $R^{30}$ , where  $R^{30}$  is alkyl, halo, pseudohalo, alkoxy, aryloxy or alkylenedioxy.
- 15 48. The pharmaceutical composition of any of claims 25-47, wherein the compound has formulae VI:



- or a pharmaceutically acceptable derivative thereof, where  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  are each independently selected from hydrogen, halo, pseudohalo, 20 hydroxyl, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, 25 alkylarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl,

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- arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxy carbonyl, aryloxy carbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl,
- 5 arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, aralkoxycarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-
- 10 dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, aminothiocabonyl,
- 15 alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminomalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl,
- 20 aryloxy carbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxy carbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio,
- 25 perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylamino sulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl,
- 30 arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl,

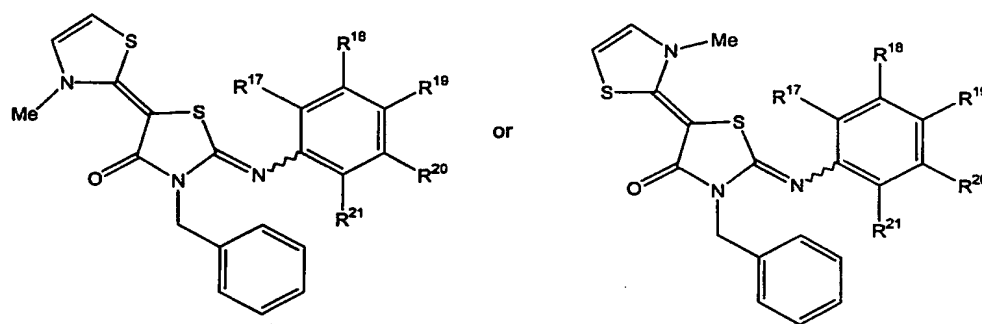
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diarylaminosulfonyl or alkylarylaminosulfonyl, or any two of R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup> and R<sup>21</sup>, which substitute adjacent carbons on the ring, together form alkylenedioxy; and

the aryl and heteroaryl groups of R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup> and R<sup>21</sup> are

- 5 unsubstituted or substituted with one or more substituents each independently selected from R<sup>30</sup>, where R<sup>30</sup> is alkyl, halo, pseudohalo, alkoxy, aryloxy or alkylenedioxy.

49. The pharmaceutical composition of any of claims 25-47, wherein the compound has formulae VII:



- 10 or a pharmaceutically acceptable derivative thereof, where  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  are each independently selected from hydrogen, halo, pseudohalo, hydroxyl, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, 15 alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, 20 aryloxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, alkylalkoxy, alkylalkoxy, arylalkoxy, aralkoxy, aralkoxy, 25 aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy,

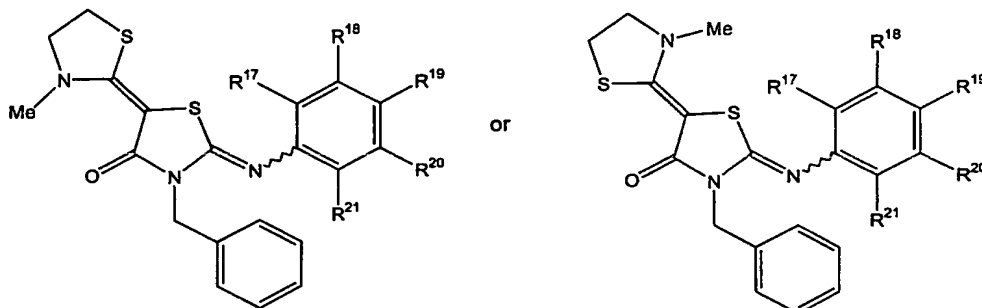


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- alkoxycarbonyloxy, aryloxy carbonyloxy, aralkoxycarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido,
- 5 N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl,
- 10 alkylarylaminalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylaminalkyl, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxy carbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxy carbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroaryl sulfonylamino,
- 15 heterocyclisulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy,
- 20 hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylamino sulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl,
- 25 diarylamino sulfonyl or alkylarylaminosulfonyl, or any two of  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$ , which substitute adjacent carbons on the ring, together form alkylenedioxy; and
- the aryl and heteroaryl groups of  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  are unsubstituted or substituted with one or more substituents each independently
- 30 selected from  $R^{30}$ , where  $R^{30}$  is alkyl, halo, pseudohalo, alkoxy, aryloxy or alkylenedioxy.

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50. The pharmaceutical composition of any of claims 25-47, wherein the compound has formulae VIII:

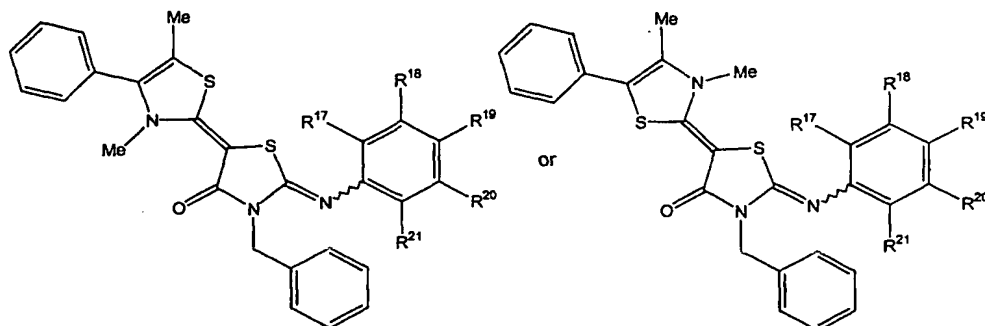


- or a pharmaceutically acceptable derivative thereof, where  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  are each independently selected from hydrogen, halo, pseudohalo, hydroxyl, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkylidiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocycloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, aralkoxycarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl,

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- alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminomethyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylaminomethyl, alkylcarbonylamino, alkoxy carbonylamino,
- 5 aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxy carbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxy carbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclisulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl,
- 10 alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxy sulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy,
- 15 diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxy sulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl, or any two of  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$ , which substitute adjacent carbons on the ring, together form
- 20 alkylenedioxy; and
- the aryl and heteroaryl groups of  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  are unsubstituted or substituted with one or more substituents each independently selected from  $R^{30}$ , where  $R^{30}$  is alkyl, halo, pseudohalo, alkoxy, aryloxy or alkylenedioxy.
- 25 51. The pharmaceutical composition of any of claims 25-47, wherein the compound has formulae IX:

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or a pharmaceutically acceptable derivative thereof, where R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup> and R<sup>21</sup> are each independently selected from hydrogen, halo, pseudohalo, hydroxyl, nitrile, nitro, formyl, mercapto, hydroxycarbonyl,

- 5** hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkylidiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl,
- 10** arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylamino carbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy,
- 15** heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, aralkoxycarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-ary lureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-ary lureido, N',N'-diary lureido, N'-ary lureido, N,N'-dialkylureido, N-alkyl-N'-ary lureido, N-aryl-N'-alkylureido, N,N'-diary lureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-ary lureido, N-alkyl-N',N'-diary lureido, N-aryl-N',N'-dialkylureido, N,N'-diary l-N'-alkylureido, N,N',N'-triary lureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl,
- 25** alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl,

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- alkylarylaminooalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino,
- 5 alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyno, isothiocyno,
- 10 alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl,
- 15 alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl, or any two of  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$ , which substitute adjacent carbons on the ring, together form alkylenedioxy; and
- the aryl and heteroaryl groups of  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  are
- 20 unsubstituted or substituted with one or more substituents each independently selected from  $R^{30}$ , where  $R^{30}$  is alkyl, halo, pseudohalo, alkoxy, aryloxy or alkylenedioxy.
52. The pharmaceutical composition of any of claims 48-51, wherein  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  are each independently selected from hydrogen,
- 25 halo, hydroxy, nitrile, nitro, hydroxycarbonyl, alkyl, haloalkyl, polyhaloalkyl, heteroaryl, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkoxy, perfluoroalkoxy, aralkoxy, amino, alkylamino, dialkylamino, haloalkylamino, alkylcarbonylamino or heterocyclyl; or any two of  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$ , which substitute adjacent carbons on the ring, form alkylenedioxy.
- 30 53. The pharmaceutical composition of any of claims 48-52, wherein  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  are each independently hydrogen, methoxy,

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- dimethylamino, NH<sub>2</sub>, benzyloxy, hydroxy, CN, isopropyl, methyl, nitro, ethylamino, trifluoromethyl, acetyl, chloro, n-propyl, ethoxy, methylcarbonylamino, CONH<sub>2</sub>, methoxycarbonyl, methylamino, trifluoromethoxy, imidazolyl, hydroxycarbonyl, isopropylamino, tert-
- 5 butylamino, 2,2,2-trifluoroethylamino, piperidinyl or morpholinyl, or any two of R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup> and R<sup>21</sup>, which substitute adjacent carbons on the ring, form methylenedioxy.

54. The pharmaceutical composition of any of claims 25-53, wherein the compound is selected from:

- 10 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-phenylimino-thiazolidine-4-one;
- 3-benzyl-2-(4-methoxyphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;
- 3-benzyl-2-(4-dimethylaminophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-
- 15 ylidene)thiazolidine-4-one;
- 2-(4-aminophenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;
- 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(quinolin-6-ylimino)-thiazolidine-4-one;
- 20 2-(2-aminophenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;
- 3-benzyl-2-(4-benzyloxyphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;
- 3-benzyl-2-(2-hydroxy-1-naphthylimino)-5-(3-methyl-3*H*-benzothiazol-2-
- 25 ylidene)thiazolidine-4-one;
- 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile;
- 3-benzyl-2-(4-hydroxy-5-isopropyl-2-methylphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;
- 30 3-benzyl-2-(2-ethylamino-5-nitrophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;

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- 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-[3-(trifluoromethyl)-phenylimino]thiazolidine-4-one;  
2-(3-acetylphenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;
- 5 3-benzyl-2-(3-chlorophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;  
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-propylphenylimino)thiazolidine-4-one;  
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(quinolin-5-ylimino)-
- 10 thiazolidine-4-one;  
3-benzyl-2-(2-ethoxyphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;  
*N*-(3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl)acetamide;
- 15 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzamide;  
3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzoic acid, methyl ester;  
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(pyridin-3-ylimino)-
- 20 thiazolidine-4-one;  
*N*-(3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethoxyphenyl)acetamide;  
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(pyridin-4-ylimino)-thiazolidine-4-one;
- 25 4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzoic acid, methyl ester;  
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-[4-(trifluoromethoxy)phenylimino]thiazolidine-4-one;  
3-benzyl-2-(1*H*-indazol-5-ylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-
- 30 thiazolidin-4-one;

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- 3-benzyl-2-(4-imidazol-1-ylphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;  
2-(benzo[1,3]dioxol-5-ylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;
- 5 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzoic acid;  
3-benzyl-2-[2-(ethylamino)phenylimino]-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidine-4-one;  
3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(methylamino)benzonitrile;
- 10 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(ethylamino)benzonitrile;  
3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(isopropylamino)benzonitrile;
- 15 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(dimethylamino)benzonitrile;  
3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(*tert*-butylamino)benzonitrile;  
3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(2,2,2-trifluoroethylamino)benzonitrile;
- 20 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-piperidin-1-ylbenzonitrile;  
2-[5-acetyl-2-(ethylamino)phenylimino]-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;
- 25 3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(quinolin-6-ylimino)-thiazolidin-4-one;  
3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-morpholin-4-ylphenylimino)thiazolidin-4-one;  
3-[3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(methylamino)benzonitrile;
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- 4-dimethylamino-3-[3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile;
- 5 3-[3-ethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(isopropylamino)benzonitrile;  
3-[3-butyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile;  
3-benzyl-5-(3-methyl-3*H*-benzoxazol-2-ylidene)-2-(quinolin-5-ylimino)-
- 10 thiazolidin-4-one;  
*N*-[4-(3'-benzyl-3-methyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-[2,5']-bithiazolyliden-2'-ylideneamino)phenyl]acetamide;  
2'-[5-acetyl-2-(ethylamino)phenylimino]-3'-benzyl-3-methyl-4-phenyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one;
- 15 3-(3'-benzyl-3-methyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-[2,5']bithiazol-yliden-2'-ylideneamino)-4-(ethylamino)benzonitrile;  
*N*-[4-(3'-benzyl-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)phenyl]acetamide;  
*N*-[4-(3'-benzyl-3-methyl-4'-oxo-[2,5']bithiazolidinyliden-2'-ylidene-
- 20 amino)phenyl]acetamide;  
3-(3'-benzyl-3,5-dimethyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-[2,5']-bithiazolyliden-2'-ylideneamino)-4-(ethylamino)benzonitrile;

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- 4-ethylamino-3-[3-benzyl-5-(3-methyl-5-chloro-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 3-phenyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-cyclohexylphenyl)imino-thiazolidine-4-one;
- 5 3-allyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-hydroxy-1-naphthyl)imino-thiazolidine-4-one;
- 4-ethylamino-3-[3-phenyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 4-ethylamino-3-[3-benzyl-5-(3-methyl-5-methoxy-3*H*-benzothiazol-2-ylidene)-
- 10 4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 3-allyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(5-quinolyl)imino-thiazolidine-4-one;
- 4-ethylamino-3-[3-allyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 15 3-phenyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-benzylimino-thiazolidine-4-one;
- 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(8-quinolyl)imino-thiazolidine-4-one;
- 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(8-hydroxy-5-
- 20 quinolyl)imino-thiazolidine-4-one;
- 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(5-isoquinolyl)imino-thiazolidine-4-one;
- 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(1-isoquinolyl)imino-thiazolidine-4-one;
- 25 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-methylcarbonylamino)phenylimino-thiazolidine-4-one;
- 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-methylcarbonyl)phenylimino-thiazolidine-4-one;
- 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-
- 30 aminocarbonyl)phenylimino-thiazolidine-4-one;

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- 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(1-naphthyl)imino-thiazolidine-4-one;
- 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-naphthyl)imino-thiazolidine-4-one;
- 5 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-pyridyl)imino-thiazolidine-4-one;
- 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-aminosulfonyl)phenylimino-thiazolidine-4-one;
- 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-methylcarbonylamino-sulfonyl)phenylimino-thiazolidine-4-one;
- 10 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(3-methylcarbonyl)phenylimino-thiazolidine-4-one;
- 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-methylcarbonylamino-5-pyridyl)imino-thiazolidine-4-one;
- 15 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-cyano-5-methylcarbonylamino-phenyl)imino-thiazolidine-4-one;
- 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-ethylamino-5-methylcarbonylphenyl)imino-thiazolidine-4-one;
- 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-methylamino-5-methylcarbonylphenyl)imino-thiazolidine-4-one;
- 20 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-trifluoromethyl-carbonylamino-phenyl)imino-thiazolidine-4-one;
- 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-ethylamino-5-methoxycarbonylphenyl)imino-thiazolidine-4-one;
- 25 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-hydroxycarbonylphenyl)imino-thiazolidine-4-one;
- 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-ethylamino-5-tert-butoxycarbonylphenyl)imino-thiazolidine-4-one;
- 4-butylamino-3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-
- 30 thiazolidin-2-ylideneamino]benzonitrile;

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- 4-benzylamino-3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-cyclopentylamino-3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 5 4-pyrrolidinylamino-3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-pyrrolidinyl-3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 4-ethylamino-3-[3-cyclohexyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 10 3-allyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(4-hydroxy-2-methyl-5-isopropylphenyl)imino-thiazolidine-4-one;  
3-cyclohexyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-hydroxy-1-naphthyl)imino-thiazolidine-4-one;
- 15 4-ethylamino-3-[3-benzyl-5-(6-fluoro-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(6-ethoxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(6-nitro-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 20 4-ethylamino-3-[3-benzyl-5-(5-trifluoromethyl-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(6-methylcarbonylamino-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 25 4-ethylamino-3-[3-benzyl-5-(5-hydroxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(6-hydroxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(5-ethylaminocarbonyloxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
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- 4-ethylamino-3-[3-benzyl-5-(5-methoxycarbonylmethoxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(5-aminocarbonylmethoxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 5 4-ethylamino-3-[3-benzyl-5-(5-(2-hydroxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(4-methoxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(4-methyl-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 10 4-ethylamino-3-[3-benzyl-5-(4-chloro-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(5-(2-chloroethylaminocarbonyloxy)-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 15 4-ethylamino-3-[3-benzyl-5-(5-(2-methylaminoethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-propyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
3-(3-pyridylmethyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(3-acetylphenyl)imino-thiazolidine-4-one;
- 20 3-(3-pyridylmethyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-ethylamino-5-acetylphenyl)imino-thiazolidine-4-one;  
4-ethylamino-3-[3-(3-pyridylmethyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 25 4-ethylamino-3-[3-(2-furylmethyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
3-(4-methoxycarbonylbenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-ethylamino-5-acetylphenyl)imino-thiazolidine-4-one;  
3-(4-hydroxycarbonylbenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(2-ethylamino-5-acetylphenyl)imino-thiazolidine-4-one;
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- 4-ethylamino-3-[3-(2-phenylethyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 4-ethylamino-3-[3-(2-(4-morpholinyl)-1-ethyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 5 3-benzyl-5-(3-methylthiazolin-2-ylidene)-2-(4-methylcarbonylaminophenyl)imino-thiazolidine-4-one;
- 3-benzyl-5-(3-methyl-4-phenylthiazol-2-ylidene)-2-(4-methylcarbonylaminophenyl)imino-thiazolidine-4-one;
- 3-benzyl-5-(3-methyl-4-phenylthiazol-2-ylidene)-2-(2-ethylamino-5-
- 10 acetylphenyl)imino-thiazolidine-4-one;
- 3-benzyl-5-(3-methylthiazol-2-ylidene)-2-(4-methylcarbonylaminophenyl)imino-thiazolidine-4-one;
- 4-ethylamino-3-[3-benzyl-5-(3-methyl-4-phenylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 15 4-ethylamino-3-[3-benzyl-5-(3-methyl-4,5-dimethylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 4-ethylamino-3-[3-benzyl-5-(3-methyl-4-phenyl-5-methylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 4-ethylamino-3-[3-benzyl-5-(3-methyl-4,5-butylenylthiazol-2-ylidene)-4-oxo-
- 20 thiazolidin-2-ylideneamino]benzonitrile;
- 4-ethylamino-3-[3-benzyl-5-(3-methyl-4-ethylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 4-ethylamino-3-[3-benzyl-5-(3-methyl-4-(4-nitrophenyl)thiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 25 4-ethylamino-3-[3-benzyl-5-(3-methyl-4-(4-fluorophenyl)thiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 4-ethylamino-3-[3-benzyl-5-(3-methyl-4-(4-chlorophenyl)thiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 4-ethylamino-3-[3-benzyl-5-(3-methyl-4-(4-methylphenyl)thiazol-2-ylidene)-4-
- 30 oxo-thiazolidin-2-ylideneamino]benzonitrile;

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- 4-ethylamino-3-[3-benzyl-5-(3-methyl-4-(4-methoxyphenyl)thiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(3-methyl-4-methyl-5-acetylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;
- 5 4-ethylamino-3-[3-benzyl-5-(3-methyl-4,5-propylenylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(3-methyl-4,5-diphenylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-benzyl-5-(3-methyl-4-methylthiazol-2-ylidene)-4-oxo-
- 10 thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-(3-pyridylmethyl)-5-(3-methyl-4,5-butylenylthiazol-2-ylidene)-4-oxo-thiazolidin-2-ylideneamino]benzonitrile; and  
3-(4-methoxycarbonylbenzyl)-5-(3-methyl-4,5-butylenylthiazol-2-ylidene)-2-(2-ethylamino-5-acetylphenyl)imino-thiazolidine-4-one.
- 15 55. The pharmaceutical composition of any of claims 25-53, wherein the compound is selected from:
- 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(quinolin-8-ylimino)thiazolidin-4-one;  
3-benzyl-2-(8-hydroxyquinolin-5-ylimino)-5-(3-methyl-3*H*-benzothiazol-2-
- 20 ylidene)thiazolidin-4-one;  
3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-butylaminobenzonitrile;  
4-benzylamino-3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile;
- 25 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-cyclopentylaminobenzonitrile;  
3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(pyrrolidin-1-ylamino)benzonitrile;  
3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-
- 30 ylideneamino]-4-pyrrolidin-1-ylbenzonitrile;

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- 3-benzyl-2-(isoquinolin-5-ylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;  
3-benzyl-2-(isoquinolin-1-ylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;
- 5 N-{4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}acetamide;  
2-(4-acetylphenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;  
4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzamide;
- 10 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(naphthalen-1-ylimino)thiazolidin-4-one;  
3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(naphthalen-2-ylimino)thiazolidin-4-one;
- 15 3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(pyridin-2-ylimino)thiazolidin-4-one;  
4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzenesulfonamide;  
N-acetyl-4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzenesulfonamide;
- 20 2-(3-acetylphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-3-pyridin-3-ylmethylthiazolidin-4-one;  
N-{5-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]pyridin-2-yl}acetamide;
- 25 N-{5-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-2-cyanophenyl}acetamide;  
2-(5-acetyl-2-ethylaminophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-3-pyridin-3-ylmethylthiazolidin-4-one;  
4-ethylamino-3-[5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-3-pyridin-3-ylmethylthiazolidin-2-ylideneamino]benzonitrile;
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- 4-ethylamino-3-[3-furan-2-ylmethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile;
- 2-(5-acetyl-2-methylaminophenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;
- 5 N-{4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-2,2,2-trifluoroacetamide;
- 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzoic acid methyl ester;
- 4-ethylamino-3-[5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-3-phenethylthiazolidin-2-ylideneamino]benzonitrile;
- 10 2-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzoic acid;
- 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzoic acid *tert*-butyl ester;
- 15 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzoic acid;
- 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(2-hydroxyethylamino)benzonitrile;
- {2-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-cyanophenylamino}acetic acid methyl ester;
- 20 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-N-ethyl-4-ethylaminobenzamide;
- {2-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-cyanophenylamino}acetic acid;
- 25 3-benzyl-2-(4-ethylaminopyridin-3-ylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;
- N-{4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-3-ethylaminophenyl}acetamide;
- 3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-(2-dimethylaminoethylamino)benzonitrile;
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- 4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-*N*-ethyl-3-ethylaminobenzamide;  
3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-*N*-(2-dimethylaminoethyl)-4-ethylaminobenzamide;
- 5 3-benzyl-2-[5-(4,5-dihydrooxazol-2-yl)-2-ethylamino-phenylimino]-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;  
3-[3-benzyl-5-(1-methyl-1*H*-quinolin-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;  
2-(5-acetyl-2-ethylaminophenylimino)-3-benzyl-5-(1-methyl-1*H*-quinolin-2-ylidene)thiazolidin-4-one;
- 10 3-benzyl-2-benzylimino-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;  
2-(3-acetylphenylimino)-3-furan-2-ylmethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;
- 15 *N*-{4-[3-furan-2-ylmethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}acetamide;  
[2-(5-acetyl-2-ethylaminophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-3-yl]acetic acid methyl ester;  
*N*-{4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-2-cyanophenyl}acetamide;
- 20 2-(5-acetyl-2-ethoxyphenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;  
2-(5-acetyl-2-hydroxyphenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;
- 25 2-(5-acetyl-2-ethylaminophenylimino)-3-benzyl-1-methyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)imidazolidin-4-one;  
4-ethylamino-3-[5-(3-methyl-3*H*-benzothiazol-2-ylidene)-3-(2-morpholin-4-ylethyl)-4-oxothiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-(4-methoxybenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-
- 30 4-oxothiazolidin-2-ylideneamino]benzonitrile;

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- 4-ethylamino-3-[3-(3-methoxybenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-(2-methoxybenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile;
- 5 N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}succinamic acid;  
N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}benzenesulfonamide;  
thiophene-2-sulfonic acid {3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}amide;
- 10 N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-3-methoxybenzamide;  
N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}methanesulfonamide;
- 15 {3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}carbamic acid ethyl ester;  
3-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-1,1-dimethylurea;  
N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-2-morpholin-4-ylacetamide;
- 20 N-{4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-2-morpholin-4-ylacetamide ;  
N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-2-dimethylaminoacetamide;
- 25 {4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}carbamic acid ethyl ester;  
N-{4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-2-dimethylaminoacetamide;  
N-{4-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}methanesulfonamide;
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- 4-ethylamino-3-[3-(3-hydroxybenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[3-(3-fluorobenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile ;
- 5 4-ethylamino-3-[3-(3-fluorobenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-3-(3-trifluoromethylbenzyl)thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-3-(2-
- 10 trifluoromethylbenzyl)thiazolidin-2-ylideneamino]benzonitrile;  
4-ethylamino-3-[5-(3-methyl-3*H*-benzothiazol-2-ylidene)-3-(3-methylbenzyl)-4-oxothiazolidin-2-ylideneamino]benzonitrile;  
N-[3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl]-2-morpholin-4-ylacetamide;
- 15 3-[3-(3-chlorobenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;  
3-[3-(3-bromobenzyl)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;  
N-[3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-
- 20 ylideneamino]-4-ethylaminophenyl]-2,2,2-trifluoroacetamide;  
N-[3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl]-2-dimethylaminoacetamide;  
4-methylpiperazine-1-carboxylic acid {3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-
- 25 ethylaminophenyl}amide;  
2-(5-amino-2-ethylaminophenylimino)-3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;  
N-[3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl]-2-(4-methylpiperazin-1-yl)acetamide;

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- N-{3-[3-benzyl-5-(5-methoxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl}-2-dimethylaminoacetamide;
- N-{3-[3-benzyl-5-(5-hydroxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl}-2-dimethylaminoacetamide;
- 5 N-(3-[3-benzyl-5-[5-(2-chloroethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylamino-phenyl)-2-dimethylaminoacetamide;
- 10 N-(3-[3-benzyl-5-[5-(2-methoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylamino-phenyl)-2-dimethylaminoacetamide;
- N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl}-2-methoxyacetamide;
- 15 N-(3-[3-benzyl-5-[5-(2-dimethylaminoethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl)-2-dimethylaminoacetamide;
- N-(3-[3-benzyl-5-[5-(2-hydroxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl)-2-dimethylamino-
- 20 acetamide;
- 2-(5-acetyl-2-ethylaminophenylimino)-5-[5-(2-chloroethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-3-furan-2-ylmethylthiazolidin-4-one;
- 2-(5-acetyl-2-ethylaminophenylimino)-3-furan-2-ylmethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;
- 25 N-(3-[3-benzyl-5-[5-(2-chloroethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl)-2-methoxyacetamide;
- N-{4-ethylamino-3-[3-furan-2-ylmethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]phenyl}-2-methoxyacetamide;
- N-(3-[3-benzyl-5-[5-(2-dimethylaminoethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl)-2-
- 30 methoxyacetamide;

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- 2-(5-acetyl-2-ethylaminophenylimino)-5-[5-(2-dimethylamino-ethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-3-furan-2-ylmethylthiazolidin-4-one;  
 N-(3-{5-[5-(2-dimethylaminoethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-3-furan-2-ylmethyl-4-oxothiazolidin-2-ylideneamino}-4-ethylaminophenyl)-2-methoxyacetamide;
- 5 acetic acid {3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenylcarbonyl}methyl ester;  
 N-{3-[3-benzyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl}-2-hydroxyacetamide;
- 10 N-(3-{3-benzyl-5-[5-(2-methoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminophenyl)-2-hydroxyacetamide;  
 2-(3-acetylphenylimino)-3-benzyl-5-[5-(2-methoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]thiazolidin-4-one;  
 2-(5-acetyl-2-ethylaminophenylimino)-3-furan-2-ylmethyl-5-[5-(2-methoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]thiazolidin-4-one;
- 15 methoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]thiazolidin-4-one;  
 N-(4-ethylamino-3-{3-furan-2-ylmethyl-5-[5-(2-methoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}phenyl)-2-methoxyacetamide;  
 2-(5-acetyl-2-ethylaminophenylimino)-3-benzyl-5-[5-(2-methoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]thiazolidin-4-one;
- 20 N-(3-{3-benzyl-5-[5-(2-methoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminophenyl)-2-methoxyacetamide;  
 N-(3-{5-[5-(2-aminoethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-3-benzyl-4-oxothiazolidin-2-ylideneamino}-4-ethylaminophenyl)-2-dimethylaminoacetamide;
- 25 2-dimethylamino-N-{3-[3-furan-2-ylmethyl-5-(5-methoxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-phenyl}acetamide;  
 3-(3'-benzyl-3,4,5-trimethyl-4'-oxo-3',4'-dihydro-3*H*-[2,5]bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile;
- 30 3-[3-benzyl-5-(3-methyl-4,5,6,7-tetrahydro-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;

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- 3-(3'-benzyl-4-ethyl-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile;  
3-[3'-benzyl-3-methyl-4-(4-nitrophenyl)-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;
- 5 3-[3'-benzyl-4-(4-fluorophenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;  
3-[3'-benzyl-4-(4-chloro-phenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;  
3-(3'-benzyl-3-methyl-4'-oxo-4-*p*-tolyl-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile;
- 10 3-[3'-benzyl-4-(4-methoxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;  
3-(5-acetyl-3'-benzyl-3,4-dimethyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile;
- 15 3-[3-benzyl-5-(3-methyl-3,4,5,6-tetrahydrocyclopentathiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;  
3-(3'-benzyl-3-methyl-4'-oxo-4,5-diphenyl-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile;  
3-(3'-benzyl-3,4-dimethyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile;
- 20 4-ethylamino-3-[5-(3-methyl-4,5,6,7-tetrahydro-3*H*-benzothiazol-2-ylidene)-4-oxo-3-pyridin-3-ylmethylthiazolidin-2-ylideneamino]benzonitrile;  
methyl 4-[2-(5-acetyl-2-ethylaminophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-3-ylmethyl]benzoate;
- 25 methyl 4-[2-(5-acetyl-2-ethylamino-phenylimino)-5-(3-methyl-4,5,6,7-tetrahydro-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-3-ylmethyl]benzoate;  
4-[2-(5-acetyl-2-ethylaminophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-3-ylmethyl]benzoic acid;
- 30 3-[3-benzyl-5-(1-methyl-4,5,6,7-tetrahydro-1*H*-thiazolo[5,4-*c*]pyridin-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;

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- methyl 3-[2-(5-acetyl-2-ethylaminophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-3-ylmethyl]benzoate ;
- 3-[2-(5-acetyl-2-ethylaminophenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-3-ylmethyl]benzoic acid;
- 5 2-(5-acetyl-2-ethylaminophenylimino)-3-benzyl-5-(3-methyl-4,5,6,7-tetrahydro-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;
- 3-(3'-benzyl-4-biphenyl-4-yl-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile;
- 3-(3'-benzyl-3-methyl-4-naphthalen-2-yl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile;
- 10 3-[3'-benzyl-4-(4-bromophenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;
- 3-[3'-benzyl-3-methyl-4-(2-nitrophenyl)-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;
- 15 2-(5-acetyl-2-ethylaminophenylimino)-5-(3-methyl-4,5,6,7-tetrahydro-3*H*-benzothiazol-2-ylidene)-3-pyridin-3-ylmethylthiazolidin-4-one;
- 3-[3'-benzyl-4-(2-methoxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;
- 3-[3'-benzyl-4-(3-fluorophenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;
- 20 3-[3'-benzyl-3-methyl-4'-oxo-4-(4-trifluoromethylphenyl)-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;
- 3-[3'-benzyl-3-methyl-4'-oxo-4-(4-trifluoromethoxyphenyl)-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;
- 25 3-[3'-benzyl-4-(2,4-dimethoxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;
- 3-(3'-benzyl-5-ethyl-3-methyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile;
- 3-[3'-benzyl-3-methyl-4'-oxo-4-(2-trifluoromethylphenyl)-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;
- 30 [2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;



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- 3-[3'-benzyl-4-(3-bromophenyl)-3,5-dimethyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;  
3-[3'-benzyl-4-(3-methoxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;
- 5 3-benzyl-2-[4-(1,1,1,3,3,3-hexafluoro-2-hydroxyisopropyl)-phenylimino]-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;  
3-(3'-benzyl-4-chloromethyl-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile;  
3'-benzyl-2'-(5-cyano-2-ethylaminophenylimino)-3-methyl-4'-oxo-3',4'-dihydro-
- 10 3*H*,2'*H*-[2,5']bithiazolylidene-4-carboxylic acid ethyl ester;  
3-(4,3'-dibenzyl-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile;  
3'-benzyl-2'-(5-cyano-2-ethylaminophenylimino)-3-methyl-4'-oxo-3',4'-dihydro-3*H*,2'*H*-[2,5']bithiazolylidene-4-carboxylic acid;
- 15 3-benzyl-2-[2-ethylamino-5-(1-hydroxyethyl)phenylimino]-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;  
3-[3'-benzyl-4-(2-hydroxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;  
3-benzyl-2-[2-ethylamino-5-(1-hydroxyiminoethyl)phenylimino]-5-(3-methyl-
- 20 3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;  
3-benzyl-2-[2-ethylamino-5-(1-methoxyiminoethyl)phenylimino]-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;  
3-benzyl-2-[5-(1-benzyloxyiminoethyl)-2-ethylaminophenylimino]-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;
- 25 3-benzyl-2-{2-ethylamino-5-[1-(phenylhydrazono)ethyl]-phenylimino}-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;  
3-(4,3'-dibenzyl-3,5-dimethyl-4'-oxo-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-2'-ylideneamino)-4-ethylaminobenzonitrile;  
3-[3-cyclohexylmethyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-
- 30 oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;

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- 3-[3'-benzyl-4-(3-hydroxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-  
[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;  
3-[3'-benzyl-4-(4-hydroxyphenyl)-3-methyl-4'-oxo-3',4'-dihydro-3*H*-  
[2,5']bithiazolyliden-2'-ylideneamino]-4-ethylaminobenzonitrile;
- 5 3-(3'-benzyl-3,4-dimethyl-4'-oxo-5-phenyl-3',4'-dihydro-3*H*-[2,5']bithiazolyliden-  
2'-ylideneamino)-4-ethylaminobenzonitrile;  
2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-3,5-dimethyl-4-phenyl-2',3'-  
dihydro-3*H*-[2,5']bithiazolyliden-4'-one;  
2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-3,4-dimethyl-5-phenyl-2',3'-
- 10 dihydro-3*H*-[2,5']bithiazolyliden-4'-one;  
2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-4-(4-methoxyphenyl)-3,5-  
dimethyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one;  
2'-(5-acetyl-2-ethylaminophenylimino)-4,3'-dibenzyl-3-methyl-2',3'-dihydro-3*H*-  
[2,5']bithiazolyliden-4'-one;
- 15 2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-4-(2-methoxyphenyl)-3,5-  
dimethyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one;  
3-[3-benzyl-5-[5-(2-dimethylaminoacetyl)-1-methyl-4,5,6,7-tetrahydro-1*H*-  
thiazolo[5,4-*c*]pyridin-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-  
ethylaminobenzonitrile;
- 20 2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-4-(3-methoxyphenyl)-3,5-  
dimethyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one;  
2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-4-(3-hydroxyphenyl)-3,5-  
dimethyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one;  
2'-(5-acetyl-2-ethylaminophenylimino)-3,3'-dibenzyl-5-methyl-4-phenyl-2',3'-
- 25 dihydro-3*H*-[2,5']bithiazolyliden-4'-one;  
N-(3-[3-benzyl-5-[5-(2-acetoxyethoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-  
oxothiazolidin-2-ylideneamino]-4-ethylaminophenyl)-2-dimethylamino-  
acetamide;  
2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-3-(2-methoxyethyl)-5-methyl-
- 30 4-phenyl-2',3'-dihydro-3*H*-[2,5']bithiazolyliden-4'-one;

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- 2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-3-(3-methoxypropyl)-5-methyl-4-phenyl-2',3'-dihydro-3*H*-[2,5]bithiazolyliden-4'-one;  
[2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-5-methyl-4'-oxo-4-phenyl-3',4'-dihydro-2'*H*-[2,5]bithiazolyliden-3-yl]acetic acid methyl ester;
- 5 [2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-5-methyl-4'-oxo-4-phenyl-3',4'-dihydro-2'*H*-[2,5]bithiazolyliden-3-yl]acetic acid;  
2-[2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-5-methyl-4'-oxo-4-phenyl-3',4'-dihydro-2'*H*-[2,5]bithiazolyliden-3-yl]ethyl acetate;  
2'-(5-acetyl-2-ethylaminophenylimino)-3'-benzyl-3-(2-hydroxyethyl)-5-methyl-
- 10 4-phenyl-2',3'-dihydro-3*H*-[2,5]bithiazolyliden-4'-one;  
N-[3-(3'-benzyl-3,5-dimethyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-[2,5]bithiazolyliden-2'-ylideneamino)-4-ethylaminophenyl]-2-methoxyacetamide;  
N-[3-(3'-benzyl-3,5-dimethyl-4'-oxo-4-phenyl-3',4'-dihydro-3*H*-
- 15 [2,5]bithiazolyliden-2'-ylideneamino)-4-ethylaminophenyl]-2-dimethylaminoacetamide;  
3-[3-cyclohexyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;  
3-[3-allyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-
- 20 ylideneamino]-4-ethylaminobenzonitrile;  
3-allyl-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-2-(quinolin-5-ylimino)thiazolidin-4-one;  
3-allyl-2-(4-hydroxy-5-isopropyl-2-methylphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;
- 25 4-ethylamino-3-[5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-3-phenylthiazolidin-2-ylideneamino]benzonitrile;  
3-cyclohexyl-2-(2-hydroxynaphthalen-1-ylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)thiazolidin-4-one;  
3-allyl-2-(2-hydroxynaphthalen-1-ylimino)-5-(3-methyl-3*H*-benzothiazol-2-
- 30 ylidene)thiazolidin-4-one;

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- 2-(4-cyclohexylphenylimino)-5-(3-methyl-3*H*-benzothiazol-2-ylidene)-3-phenylthiazolidin-4-one;
- 3-[3-benzyl-5-(6-fluoro-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;
- 5 3-[3-benzyl-5-(5-chloro-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;
- 3-[3-benzyl-5-(6-ethoxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;
- 4-ethylamino-3-[5-(3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxo-3-propylthiazolidin-2-ylideneamino]benzonitrile;
- 10 3-[3-benzyl-5-(3-methyl-6-nitro-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;
- N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}acetamide;
- 15 3-[3-benzyl-5-(6-hydroxy-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;
- ethylcarbamic acid 2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yl ester;
- {2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yloxy}acetic acid methyl ester;
- 20 2-[2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yloxy}acetamide;
- (2-chloroethyl)carbamic acid 2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yl ester;
- 25 3-[3-benzyl-5-[3-methyl-5-(2-methylaminoethoxy)-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;
- 3-[3-benzyl-5-[5-(3-hydroxypropoxy)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;

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- (3-chloropropyl)carbamic acid 2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yl ester;
- 3-(3-benzyl-5-[3-methyl-5-[2-(4-methylpiperazin-1-yl)-ethoxy]-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino)-4-ethylaminobenzonitrile;
- 5 3-{3-benzyl-5-[3-methyl-5-(2-piperidin-4-ylethoxy)-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile;
- 3-{3-benzyl-5-[5-(2-dimethylaminoethoxy)-3-methyl-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile;
- 10 {2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yloxy}acetic acid;
- 3-{3-benzyl-5-[6-(2-hydroxyethoxy)-3-methyl-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile;
- 15 3-{3-benzyl-5-[6-(2-methoxyethoxy)-3-methyl-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile;
- 3-{3-benzyl-5-[3-methyl-6-(2-morpholin-4-ylethoxy)-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile;
- 3-{3-benzyl-5-[5-(2-methoxyethoxy)-3-methyl-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile;
- 20 3-{3-benzyl-5-[3-methyl-4-methoxy-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile;
- 3-{3-benzyl-5-[3-methyl-4-methyl-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile;
- 25 3-{3-benzyl-5-[3-methyl-4-chloro-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile;
- 3-{3-benzyl-5-[3-methyl-6-trifluoromethoxy-3H-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile;
- 3-[3-benzyl-5-(3,5,6-trimethyl-3H-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;
- 30

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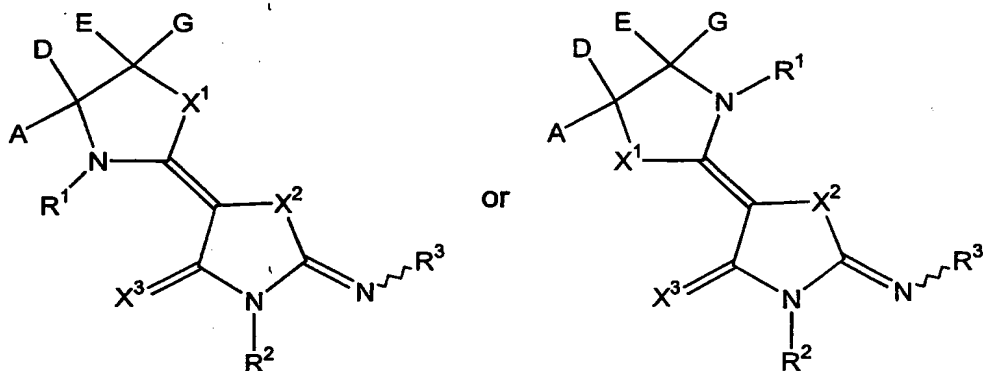
- 3-[3-benzyl-5-(3-methyl-5-acetamido-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;  
 N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazilidin-6-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yl}-2,2,2-trifluoroacetamide;
- 5 3-[5-(6-amino-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;  
 N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}-N',N''-di(tert-butoxycarbonyl)guanidine;
- 10 2-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazilidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}-1,1,-dimethylurea;  
 N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazilidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yl}-2,2,2-trifluoroacetamide;  
 3-[5-(5-amino-3-methyl-3*H*-benzothiazol-2-ylidene)-4-oxothiazolidin-2-
- 15 ylideneamino]-4-ethylaminobenzonitrile;  
 {2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazilidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}carbamic acid ethyl ester;  
 N-[2-(3-benzyl-2-{5-cyano-2-[ethyl-(2-morpholin-ylethyl)amino]phenylimino)-4-oxothiazilidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl]-2,2,2-
- 20 trifluoroacetamide;  
 N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazilidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}-2,2,2-trifluoro-N-(2-morpholin-4ylethyl)acetamide;  
 3-[3-benzyl-5-[3-methyl-6-(2-morpholin-4-yl-ethylamino)-3*H*-benzothiazol-2-
- 25 ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;  
 3-[3-benzyl-5-[3-methyl-6-(2-piperidin-1-yl-ethylamino)-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino]-4-ethylaminobenzonitrile;  
 N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazilidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-5-yl}-2,2,2-trifluoro-N-(2-morpholin-
- 30 4ylethyl)acetamide;

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- 3-{3-benzyl-5-[3-methyl-5-(2-morpholin-4-yl-ethylamino)-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile;  
 N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}guanidine;
- 5 3-{3-benzyl-5-[3-methyl-6-(4-trifluoromethylbenzylamino)-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-ethylaminobenzonitrile;  
 N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}-N-(3-fluoropropyl)-2,2,2-trifluoroacetamide;
- 10 N-{2-[3-benzyl-2-(5-cyano-2-ethylaminophenylimino)-4-oxothiazolidin-5-ylidene]-3-methyl-2,3-dihydrobenzothiazol-6-yl}-N-(3-cyanopropyl)-2,2,2-trifluoroacetamide;  
 3-{3-benzyl-5-[6-(3-cyanopropylamino)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-(ethylamino)benzonitrile;
- 15 3-{3-benzyl-5-[6-(3-hydroxypropylamino)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-(ethylamino)benzonitrile; and  
 3-{3-benzyl-5-[6-(2-methoxyethylamino)-3-methyl-3*H*-benzothiazol-2-ylidene]-4-oxothiazolidin-2-ylideneamino}-4-(ethylamino)benzonitrile.

56. An article of manufacture, comprising packaging material, a

20 compound formulae I:



or a pharmaceutically acceptable derivative thereof, wherein:

A, D, E and G are selected from (i) or (ii) as follows:

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(i) A and G are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroarylum, substituted or unsubstituted heteroarylumalkyl, halo, pseudohalo, OR<sup>10</sup>, SR<sup>10</sup>, S(=O)R<sup>13</sup>, S(=O)<sub>2</sub>R<sup>13</sup>, NR<sup>11</sup>R<sup>12</sup> and C(=J)R<sup>13</sup>, or A and G together form substituted or unsubstituted alkylene, substituted or unsubstituted azaalkylene, substituted or unsubstituted oxaalkylene, substituted or unsubstituted thiaalkylene, substituted or unsubstituted alkenylene, substituted or unsubstituted alkynylene, substituted or unsubstituted 1,3-butadienylene, substituted or unsubstituted 1-aza-1,3-butadienylene, or substituted or unsubstituted 2-aza-1,3-butadienylene;

D and E are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo and pseudohalo or D and E together form a bond; or

(ii) A and D; or E and G; together form substituted or unsubstituted alkylene, substituted or unsubstituted azaalkylene, substituted or unsubstituted oxaalkylene, or substituted or unsubstituted thiaalkylene; and the others of A, D, E and G are selected as in (i);



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$X^1$  and  $X^2$  are each independently selected from O, S, S(=O), S(=O)<sub>2</sub>, Se, NR<sup>5</sup>, CR<sup>6</sup>R<sup>7</sup> and CR<sup>8</sup>=CR<sup>9</sup>;

$X^3$  is O, S, Se, NR<sup>5</sup> or CR<sup>6</sup>R<sup>7</sup>;

$R^1$  and  $R^2$  are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroarylium, substituted or unsubstituted heteroaryliumalkyl, OR<sup>10</sup>, SR<sup>10</sup>, S(=O)R<sup>13</sup>, S(=O)<sub>2</sub>R<sup>13</sup>, NR<sup>11</sup>R<sup>12</sup> and C(=J)R<sup>13</sup>;

$R^3$  is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylium, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroaryliumalkyl, OR<sup>10</sup>, SR<sup>10</sup>, S(=O)R<sup>13</sup>, S(=O)<sub>2</sub>R<sup>13</sup>, NR<sup>11</sup>R<sup>12</sup> and C(=J)R<sup>13</sup>;

where

$R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$  and  $R^9$  are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo, pseudohalo, OR<sup>10</sup>, NR<sup>14</sup>R<sup>15</sup> and C(=J)R<sup>13</sup>;

$R^{10}$ ,  $R^{11}$  and  $R^{12}$  are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or

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- unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted
- 5 aralkyl, substituted or unsubstituted heteroaralkyl or  $C(=J)R^{13}$ ;  
 J is O, S or  $NR^{14}$ ;  
 $R^{13}$  is selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
- 10 heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, pseudohalo,  $OR^{16}$  and  $NR^{14}R^{15}$ ;  
 $R^{14}$ ,  $R^{15}$  and  $R^{16}$  are each independently selected from hydrogen, alkyl,
- 15 alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl;  
 where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclalkyl, aryl, heteroaryl, heteroarylium, aralkyl, heteroaralkyl and heteroaryliumalkyl moieties of A, D, E, G,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^5$ ,  $R^6$ ,
- 20  $R^7$ ,  $R^8$ ,  $R^9$ ,  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$  and  $R^{13}$  are unsubstituted or substituted with one or more substituents each independently selected from  $Q^1$ , where  $Q^1$  is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl
- 25 containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxy carbonyl, aryloxy carbonylalkyl, aralkoxycarbonyl,
- 30 aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl,

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- arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, aralkoxy carbonyloxy,
- 5 aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, imino, hydroxyimino, alkoxyimino, aryloxyimino, aralkoxyimino, alkylazo, arylazo, aralkylazo, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl,
- 15 arylaminoalkyl, diarylaminoalkyl, alkylarylaminominoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylaminomino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxy carbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxy carbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxy carbonylamino, alkylsulfonylamino, arylsulfonylamino,
- 20 heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy,
- 25 alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl,
- 30 dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two  $Q^1$  groups, which substitute atoms in a 1,2 or

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1,3 arrangement, together form alkylendioxy, thioalkylenoxy or alkylenedithioxy where y is 1 or 2; or two Q<sup>1</sup> groups, which substitute the same atom, together form alkylene; and

- each Q<sup>1</sup> is independently unsubstituted or substituted with one or more
- 5 substituents each independently selected from Q<sup>2</sup>;
- each Q<sup>2</sup> is independently halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl,
- 10 cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkylidiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl,
- 15 arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-
- 25 diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl,
- 30 alkylarylaminalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino,

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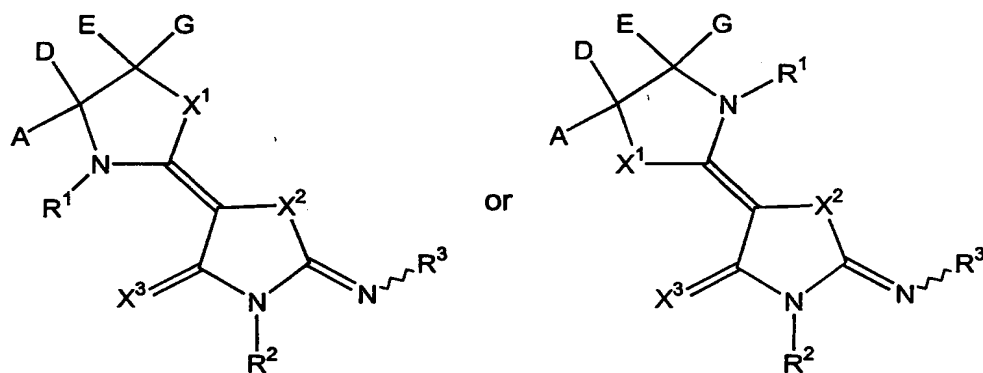
- aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclisulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy,
- 5  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy,
- 10 alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two  $Q^2$  groups, which
- 15 substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy, thioalkylenoxy or alkylenedithioxy where y is 1 or 2; or two  $Q^2$  groups, which substitute the same atom, together form alkylene;
- each  $Q^2$  is independently unsubstituted or substituted with one or more substituents each independently selected from alkyl, halo and pseudohalo;
- 20  $R^{50}$  is hydroxy, alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or  $-NR^{70}R^{71}$ , where  $R^{70}$  and  $R^{71}$  are each independently hydrogen, alkyl, aralkyl, aryl, heteroaryl, heteroaralkyl or heterocyclyl, or  $R^{70}$  and  $R^{71}$  together form alkylene, azaalkylene, oxaalkylene or thiaalkylene;
- $R^{51}$ ,  $R^{52}$  and  $R^{53}$  are each independently hydrogen, alkyl, aryl, aralkyl,
- 25 heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl;
- $R^{60}$  is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl; and
- $R^{63}$  is alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or  $-NR^{70}R^{71}$ ;
- with the proviso that when  $R^3$  is substituted or unsubstituted
- 30 heteroarylium then the heteroatom substituent is not alkyl or aryl;

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which is effective for modulating the activity of a nuclear receptor or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity is implicated, within the packaging material, and a

- 5 label that indicates that the compound or pharmaceutically acceptable derivative thereof is used for modulating the activity of a nuclear receptor or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity is implicated.

- 10 57. A method of treating, preventing, or ameliorating the symptoms of a disease or disorder that is modulated or otherwise affected by nuclear receptor activity or in which nuclear receptor activity is implicated, comprising administering to a subject in need thereof an effective amount of a compound formulae I:



or a pharmaceutically acceptable derivative thereof, wherein:

A, D, E and G are selected from (i) or (ii) as follows:

- (i) A and G are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl,
- 20

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- substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroarylium, substituted or unsubstituted heteroaryliumalkyl, halo, pseudohalo,  $OR^{10}$ ,  $SR^{10}$ ,  $S(=O)R^{13}$ ,  $S(=O)_2R^{13}$ ,  $NR^{11}R^{12}$  and  $C(=J)R^{13}$ , or A and G together form substituted or unsubstituted alkylene,
- 5 substituted or unsubstituted azaalkylene, substituted or unsubstituted oxaalkylene, substituted or unsubstituted thiaalkylene, substituted or unsubstituted alkenylene, substituted or unsubstituted alkynylene, substituted or unsubstituted 1,3-butadienylene, substituted or unsubstituted 1-aza-1,3-butadienylene, or substituted or unsubstituted
- 10 2-aza-1,3-butadienylene;
- D and E are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or
- 15 unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo and pseudohalo or D and E together form a bond; or
- 20 (ii) A and D; or E and G; together form substituted or unsubstituted alkylene, substituted or unsubstituted azaalkylene, substituted or unsubstituted oxaalkylene, or substituted or unsubstituted thiaalkylene; and the others of A, D, E and G are selected as in (i);
- $X^1$  and  $X^2$  are each independently selected from O, S,  $S(=O)$ ,  $S(=O)_2$ ,
- 25 Se,  $NR^5$ ,  $CR^6R^7$  and  $CR^8=CR^9$ ;
- $X^3$  is O, S, Se,  $NR^5$  or  $CR^6R^7$ ;
- $R^1$  and  $R^2$  are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or
- 30 unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted

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aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroarylium, substituted or unsubstituted heteroaryliumalkyl,  $OR^{10}$ ,  $SR^{10}$ ,  $S(=O)R^{13}$ ,  $S(=O)_2R^{13}$ ,  $NR^{11}R^{12}$  and  $C(=J)R^{13}$ ;

- 5  $R^3$  is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,
- 10 substituted or unsubstituted heteroarylium, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroaryliumalkyl,  $OR^{10}$ ,  $SR^{10}$ ,  $S(=O)R^{13}$ ,  $S(=O)_2R^{13}$ ,  $NR^{11}R^{12}$  and  $C(=J)R^{13}$ ;
- where

- $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$  and  $R^9$  are each independently selected from hydrogen,
- 15 substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or
- 20 unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo, pseudohalo,  $OR^{10}$ ,  $NR^{14}R^{15}$  and  $C(=J)R^{13}$ ;

- $R^{10}$ ,  $R^{11}$  and  $R^{12}$  are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or
- 25 unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl or  $C(=J)R^{13}$ ;

J is O, S or  $NR^{14}$ ;

- 30  $R^{13}$  is selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl,



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- substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, pseudohalo, OR<sup>16</sup> and NR<sup>14</sup>R<sup>15</sup>;
- 5     R<sup>14</sup>, R<sup>15</sup> and R<sup>16</sup> are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl;
- where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl,
- 10    cycloalkylalkyl, heterocyclalkyl, aryl, heteroaryl, heteroarylium, aralkyl, heteroaralkyl and heteroaryliumalkyl moieties of A, D, E, G, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup> and R<sup>13</sup> are unsubstituted or substituted with one or more substituents each independently selected from Q<sup>1</sup>, where Q<sup>1</sup> is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto,
- 15    hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkylidene, arylalkylidene,
- 20    alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxy carbonyl, aryloxy carbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy,
- 25    heterocyclcyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido,
- 30    ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-

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- arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, imino, hydroxyimino, alkoxyimino, aryloxyimino, aralkoxyimino,
- 5 alkylazo, arylazo, aralkylazo, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminomalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylaminom, alkylcarbonylamino, alkoxy carbonylamino, aralkoxy carbonylamino, arylcarbonylamino,
- 10 arylcarbonylaminoalkyl, aryloxy carbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxy carbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclisulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl,
- 15 hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyno, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxy sulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylamino sulfonyloxy,
- 20 alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxy sulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylamino sulfonyl or alkylarylaminosulfonyl; or two  $Q^1$  groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy, thioalkylenoxy or
- 25 alkylenedithioxy where y is 1 or 2; or two  $Q^1$  groups, which substitute the same atom, together form alkylene; and
- each  $Q^1$  is independently unsubstituted or substituted with one or more substituents each independently selected from  $Q^2$ ;
- each  $Q^2$  is independently halo, pseudohalo, hydroxy, oxo, thia, nitrile,
- 30 nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2

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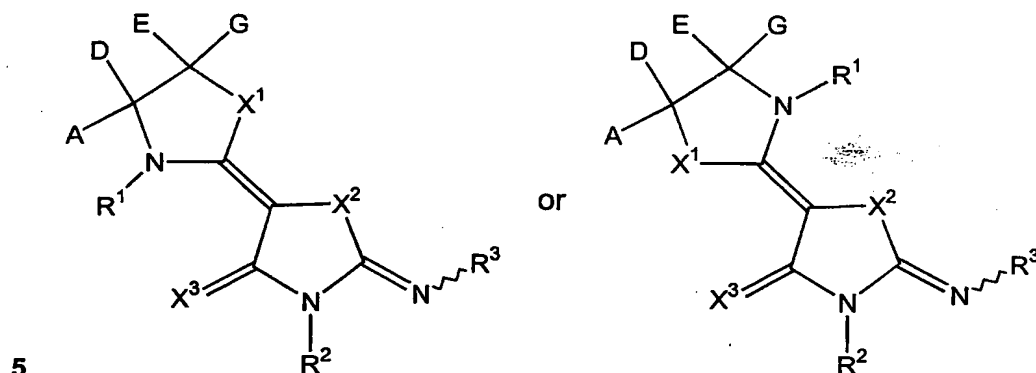
- double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkylidiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl,
- 5 heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxy carbonyl, aryloxy carbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy,
- 10 perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, aralkoxy carbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido,
- 15 N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-trialkylureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl,
- 20 alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylaminalkyl, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl,
- 25 aryloxy carbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxy carbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio,
- 30 perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy,

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- hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylamino sulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl,
- 5 alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylamino sulfonyl or alkylarylaminosulfonyl; or two Q<sup>2</sup> groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy, thioalkylenoxy or alkylenedithioxy where y is 1 or 2; or two Q<sup>2</sup> groups, which substitute the same atom, together form alkylene;
- 10 each Q<sup>2</sup> is independently unsubstituted or substituted with one or more substituents each independently selected from alkyl, halo and pseudohalo; R<sup>50</sup> is hydroxy, alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or -NR<sup>70</sup>R<sup>71</sup>, where R<sup>70</sup> and R<sup>71</sup> are each independently hydrogen, alkyl, aralkyl, aryl, heteroaryl, heteroaralkyl or heterocyclyl, or R<sup>70</sup> and R<sup>71</sup> together form
- 15 alkylene, azaalkylene, oxaalkylene or thiaalkylene; R<sup>51</sup>, R<sup>52</sup> and R<sup>53</sup> are each independently hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl; R<sup>60</sup> is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl; and
- 20 R<sup>63</sup> is alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or -NR<sup>70</sup>R<sup>71</sup>.
58. The method of claim 57, wherein the disease or disorder is selected from hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin
- 25 conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, hyperlipidemia, cholestasis, peripheral occlusive disease, ischemic stroke, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous
- 30 membrane, and cardiovascular disorders.

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59. A method of treating, preventing, or ameliorating one or more symptoms of a disease or disorder which is affected by cholesterol, triglyceride, or bile acid levels, comprising administering to a subject in need thereof an effective amount of a compound formulae I:



or a pharmaceutically acceptable derivative thereof, wherein:

A, D, E and G are selected from (i) or (ii) as follows:

- (i) A and G are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroarylium, substituted or unsubstituted heteroaryliumalkyl, halo, pseudohalo, OR<sup>10</sup>, SR<sup>10</sup>, S(=O)R<sup>13</sup>, S(=O)<sub>2</sub>R<sup>13</sup>, NR<sup>11</sup>R<sup>12</sup> and C(=J)R<sup>13</sup>, or A and G together form substituted or unsubstituted alkylene, substituted or unsubstituted azaalkylene, substituted or unsubstituted oxaalkylene, substituted or unsubstituted thiaalkylene, substituted or unsubstituted alkenylene, substituted or unsubstituted alkynylene, substituted or unsubstituted 1,3-butadienylene, substituted or unsubstituted 1-aza-1,3-butadienylene, or substituted or unsubstituted 2-aza-1,3-butadienylene;

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- D and E are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo and pseudohalo or D and E together form a bond; or
- (ii) A and D; or E and G; together form substituted or unsubstituted alkylene, substituted or unsubstituted azaalkylene, substituted or unsubstituted oxaalkylene, or substituted or unsubstituted thiaalkylene; and the others of A, D, E and G are selected as in (i);  
 $X^1$  and  $X^2$  are each independently selected from O, S,  $S(=O)$ ,  $S(=O)_2$ .
- Se,  $NR^5$ ,  $CR^6R^7$  and  $CR^8=CR^9$ ;  
 $X^3$  is O, S, Se,  $NR^5$  or  $CR^6R^7$ ;  
 $R^1$  and  $R^2$  are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroarylium, substituted or unsubstituted heteroaryliumalkyl,  $OR^{10}$ ,  $SR^{10}$ ,
- $S(=O)R^{13}$ ,  $S(=O)_2R^{13}$ ,  $NR^{11}R^{12}$  and  $C(=J)R^{13}$ ;  
 $R^3$  is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylium, substituted or unsubstituted

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aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroaryliumalkyl,  $OR^{10}$ ,  $SR^{10}$ ,  $S(=O)R^{13}$ ,  $S(=O)_2R^{13}$ ,  $NR^{11}R^{12}$  and  $C(=J)R^{13}$ ; where

- $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$  and  $R^9$  are each independently selected from hydrogen, 5 substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or 10 unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo, pseudohalo,  $OR^{10}$ ,  $NR^{14}R^{15}$  and  $C(=J)R^{13}$ ;

- $R^{10}$ ,  $R^{11}$  and  $R^{12}$  are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or 15 unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl or  $C(=J)R^{13}$ ;

J is O, S or  $NR^{14}$ ;

- 20  $R^{13}$  is selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted 25 or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, pseudohalo,  $OR^{16}$  and  $NR^{14}R^{15}$ ;

$R^{14}$ ,  $R^{15}$  and  $R^{16}$  are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl;

- 30 where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclalkyl, aryl, heteroaryl, heteroarylium, aralkyl,

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- heteroaralkyl and heteroaryliumalkyl moieties of A, D, E, G, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup> and R<sup>13</sup> are unsubstituted or substituted with one or more substituents each independently selected from Q<sup>1</sup>, where Q<sup>1</sup> is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto,
- 5 hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkylidiarylsilyl, triarylsilyl, alkylidene, arylalkylidene,
  - 10 alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxy carbonyl, aryloxy carbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy,
  - 15 heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido,
  - 20 ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino,
  - 25 arylamidino, imino, hydroxyimino, alkoxyimino, aryloxyimino, aralkoxyimino, alkylazo, arylazo, aralkylazo, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminominoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylaminomino, alkylcarbonylamino,
  - 30 alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxy carbonylaminoalkyl, aryloxyarylcarbonylamino,



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- aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclisulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl,
- 5 hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy,
- 10 alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two  $Q^1$  groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy, thioalkylenoxy or
- 15 alkylenedithioxy where y is 1 or 2; or two  $Q^1$  groups, which substitute the same atom, together form alkylene; and
- each  $Q^1$  is independently unsubstituted or substituted with one or more substituents each independently selected from  $Q^2$ ;
- each  $Q^2$  is independently halo, pseudohalo, hydroxy, oxo, thia, nitrile,
- 20 nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkylidiarylsilyl,
- 25 triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy,
- 30 aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy,

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- arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy,  
 aralkoxy carbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy,  
 dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy,  
 guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido,  
 5 N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido,  
 N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-  
 diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-  
 diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-  
 triarylureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl,  
 10 alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl,  
 alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl,  
 alkylarylaminominoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino,  
 diarylamino, alkylarylaminomino, alkylcarbonylamino, alkoxycarbonylamino,  
 aralkoxy carbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl,  
 15 aryloxy carbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxy carbonylamino,  
 alkylsulfonylamino, arylsulfonylamino, heteroaryl sulfonylamino,  
 heterocyclisulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  
 $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl,  
 alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio,  
 20 perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyno, isothiocyano,  
 alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy,  
 hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy,  
 alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy,  
 diarylamino sulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl,  
 25 arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl,  
 alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl,  
 diarylamino sulfonyl or alkylarylaminosulfonyl; or two  $Q^2$  groups, which  
 substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy,  
 thioalkylenoxy or alkylenedithioxy where y is 1 or 2; or two  $Q^2$  groups, which  
 30 substitute the same atom, together form alkylene;

each Q<sup>2</sup> is independently unsubstituted or substituted with one or more substituents each independently selected from alkyl, halo and pseudohalo;

$R^{50}$  is hydroxy, alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or  $-NR^{70}R^{71}$ , where  $R^{70}$  and  $R^{71}$  are each independently hydrogen, alkyl, aralkyl.

5 aryl, heteroaryl, heteroaralkyl or heterocyclyl, or R<sup>70</sup> and R<sup>71</sup> together form alkylene, azaalkylene, oxaalkylene or thiaalkylene;

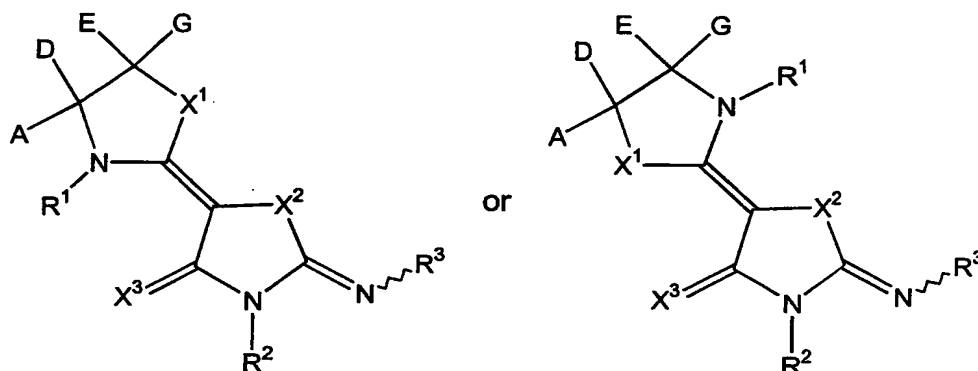
**R<sup>51</sup>, R<sup>52</sup> and R<sup>53</sup> are each independently hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl;**

**R<sup>60</sup> is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl,**

**10** heterocyclyl or heterocyclylalkyl; and

**R<sup>63</sup> is alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or -NR<sup>70</sup>R<sup>71</sup>.**

60. A method of modulating nuclear receptor activity, comprising contacting the nuclear receptor with a compound formulae I:



**15** or a pharmaceutically acceptable derivative thereof, wherein:

**A, D, E and G are selected from (i) or (ii) as follows:**

(i) A and G are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted

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- heteroarylium, substituted or unsubstituted heteroaryliumalkyl, halo, pseudohalo,  $OR^{10}$ ,  $SR^{10}$ ,  $S(=O)R^{13}$ ,  $S(=O)_2R^{13}$ ,  $NR^{11}R^{12}$  and  $C(=J)R^{13}$ , or A and G together form substituted or unsubstituted alkylene, substituted or unsubstituted azaalkylene, substituted or unsubstituted oxaalkylene, substituted or unsubstituted thiaalkylene, substituted or unsubstituted alkenylene, substituted or unsubstituted alkynylene, substituted or unsubstituted 1,3-butadienylene, substituted or unsubstituted 1-aza-1,3-butadienylene, or substituted or unsubstituted 2-aza-1,3-butadienylene;
- 10 D and E are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo and pseudohalo or D and E together form a bond; or
- 15 (ii) A and D; or E and G; together form substituted or unsubstituted alkylene, substituted or unsubstituted azaalkylene, substituted or unsubstituted oxaalkylene, or substituted or unsubstituted thiaalkylene; and the others of A, D, E and G are selected as in (i);
- $X^1$  and  $X^2$  are each independently selected from O, S,  $S(=O)$ ,  $S(=O)_2$ , Se,  $NR^5$ ,  $CR^6R^7$  and  $CR^8=CR^9$ ;
- 20  $X^3$  is O, S, Se,  $NR^5$  or  $CR^6R^7$ ;
- $R^1$  and  $R^2$  are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted
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aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroarylium, substituted or unsubstituted heteroaryliumalkyl,  $OR^{10}$ ,  $SR^{10}$ ,  $S(=O)R^{13}$ ,  $S(=O)_2R^{13}$ ,  $NR^{11}R^{12}$  and  $C(=J)R^{13}$ ;

- $R^3$  is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylium, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroaryliumalkyl,  $OR^{10}$ ,  $SR^{10}$ ,  $S(=O)R^{13}$ ,  $S(=O)_2R^{13}$ ,  $NR^{11}R^{12}$  and  $C(=J)R^{13}$ ; where

- $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$  and  $R^9$  are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo, pseudohalo,  $OR^{10}$ ,  $NR^{14}R^{15}$  and  $C(=J)R^{13}$ ;

- $R^{10}$ ,  $R^{11}$  and  $R^{12}$  are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl or  $C(=J)R^{13}$ ;

J is O, S or  $NR^{14}$ ;

- $R^{13}$  is selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted



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- dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, imino, hydroxyimino, alkoxyimino, aryloxyimino, aralkoxyimino, alkylazo, arylazo, aralkylazo, aminothiocarbonyl, alkylaminothiocarbonyl,
- 5 arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminominoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylaminomino, alkylcarbonylamino, alkoxy carbonylamino, aralkoxy carbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxy carbonylaminoalkyl, aryloxyarylcarbonylamino,
- 10 aryloxy carbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroaryl sulfonylamino, heterocyclisulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio,
- 15 hydroxycarbonylalkylthio, thiocyno, isothiocyno, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxy sulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylamino sulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl,
- 20 hydroxysulfonyl, alkoxy sulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylamino sulfonyl or alkylarylaminosulfonyl; or two  $Q^1$  groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy, thioalkylenoxy or alkylenedithioxy where y is 1 or 2; or two  $Q^1$  groups, which substitute the
- 25 same atom, together form alkylene; and
- each  $Q^1$  is independently unsubstituted or substituted with one or more substituents each independently selected from  $Q^2$ ;
- each  $Q^2$  is independently halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl,
- 30 haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl,

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- cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyldiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl,
- 5 aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy,
- 10 arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido,
- 15 N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl,
- 20 alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcabonylamino, aryloxycarbonylamino,
- 25 alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano,
- 30 alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy,



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alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylamino sulfonyloxy, alkylarylamino sulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl,

- 5 diarylamino sulfonyl or alkylarylamino sulfonyl; or two  $Q^2$  groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy, thioalkylenoxy or alkylenedithioxy where y is 1 or 2; or two  $Q^2$  groups, which substitute the same atom, together form alkylene;

each  $Q^2$  is independently unsubstituted or substituted with one or more

- 10 substituents each independently selected from alkyl, halo and pseudohalo;

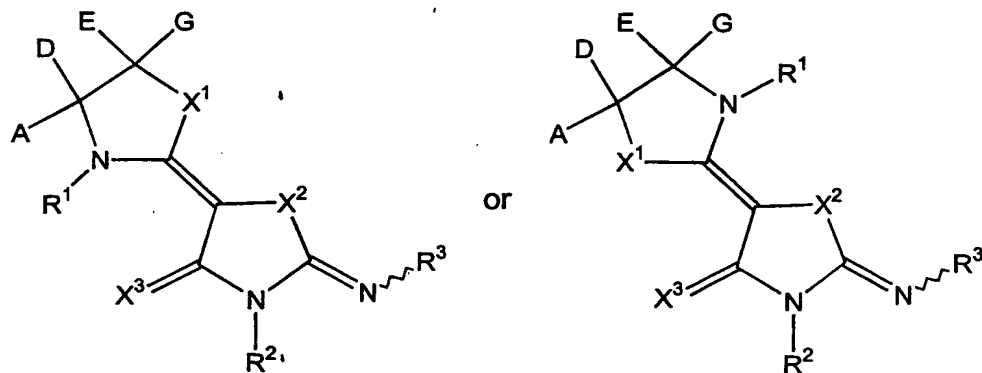
$R^{50}$  is hydroxy, alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or  $-NR^{70}R^{71}$ , where  $R^{70}$  and  $R^{71}$  are each independently hydrogen, alkyl, aralkyl, aryl, heteroaryl, heteroaralkyl or heterocyclyl, or  $R^{70}$  and  $R^{71}$  together form alkylene, azaalkylene, oxaalkylene or thiaalkylene;

- 15  $R^{51}$ ,  $R^{52}$  and  $R^{53}$  are each independently hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclalkyl;

$R^{60}$  is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclalkyl; and

$R^{63}$  is alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or  $-NR^{70}R^{71}$ .

- 20 61. A method of treating, preventing, or ameliorating one or more symptoms of cholestasis in a subject in need thereof, comprising administering an effective amount of a compound of formulae I:



or a pharmaceutically acceptable derivative thereof, wherein:

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A, D, E and G are selected from (i) or (ii) as follows:

- (i) A and G are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted heteroarylium, substituted or unsubstituted heteroaryliumalkyl, halo, pseudohalo,  $OR^{10}$ ,  $SR^{10}$ ,  $S(=O)R^{13}$ ,  $S(=O)_2R^{13}$ ,  $NR^{11}R^{12}$  and  $C(=J)R^{13}$ , or A and G together form substituted or unsubstituted alkylene, substituted or unsubstituted azaalkylene, substituted or unsubstituted oxaalkylene, substituted or unsubstituted thiaalkylene, substituted or unsubstituted alkenylene, substituted or unsubstituted alkynylene, substituted or unsubstituted 1,3-butadienylene, substituted or unsubstituted 1-aza-1,3-butadienylene, or substituted or unsubstituted 2-aza-1,3-butadienylene;
- D and E are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo and pseudohalo or D and E together form a bond; or
- (ii) A and D; or E and G; together form substituted or unsubstituted alkylene, substituted or unsubstituted azaalkylene, substituted or unsubstituted oxaalkylene, or substituted or unsubstituted thiaalkylene; and the others of A, D, E and G are selected as in (i);

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$X^1$  and  $X^2$  are each independently selected from O, S, S(=O), S(=O)<sub>2</sub>, Se, NR<sup>5</sup>, CR<sup>6</sup>R<sup>7</sup> and CR<sup>8</sup>=CR<sup>9</sup>;

$X^3$  is O, S, Se, NR<sup>5</sup> or CR<sup>6</sup>R<sup>7</sup>;

R<sup>1</sup> and R<sup>2</sup> are each independently selected from hydrogen, substituted  
5 or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or  
unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or  
unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl,  
substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted  
aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted  
10 aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted  
heteroarylium, substituted or unsubstituted heteroaryliumalkyl, OR<sup>10</sup>, SR<sup>10</sup>,  
S(=O)R<sup>13</sup>, S(=O)<sub>2</sub>R<sup>13</sup>, NR<sup>11</sup>R<sup>12</sup> and C(=J)R<sup>13</sup>;

R<sup>3</sup> is hydrogen, substituted or unsubstituted alkyl, substituted or  
unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or  
15 unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted  
or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl,  
substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,  
substituted or unsubstituted heteroarylium, substituted or unsubstituted  
aralkyl, substituted or unsubstituted heteroaralkyl, substituted or unsubstituted  
20 heteroaryliumalkyl, OR<sup>10</sup>, SR<sup>10</sup>, S(=O)R<sup>13</sup>, S(=O)<sub>2</sub>R<sup>13</sup>, NR<sup>11</sup>R<sup>12</sup> and C(=J)R<sup>13</sup>;  
where

R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> are each independently selected from hydrogen,  
substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl,  
substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl,  
25 substituted or unsubstituted heterocyclyl, substituted or unsubstituted  
cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or  
unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or  
unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo,  
pseudohalo, OR<sup>10</sup>, NR<sup>14</sup>R<sup>15</sup> and C(=J)R<sup>13</sup>;

30 R<sup>10</sup>, R<sup>11</sup> and R<sup>12</sup> are each independently hydrogen, substituted or  
unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or

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- unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted
- 5 aralkyl, substituted or unsubstituted heteroaralkyl or  $C(=J)R^{13}$ ;  
 J is O, S or  $NR^{14}$ ;  
 $R^{13}$  is selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
- 10 heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, pseudohalo,  $OR^{16}$  and  $NR^{14}R^{15}$ ;  
 $R^{14}$ ,  $R^{15}$  and  $R^{16}$  are each independently selected from hydrogen, alkyl,
- 15 alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl;  
 where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclalkyl, aryl, heteroaryl, heteroarylum, aralkyl, heteroaralkyl and heteroarylumalkyl moieties of A, D, E, G,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^5$ ,  $R^6$ ,
- 20  $R^7$ ,  $R^8$ ,  $R^9$ ,  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$  and  $R^{13}$  are unsubstituted or substituted with one or more substituents each independently selected from  $Q^1$ , where  $Q^1$  is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl
- 25 containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxy carbonyl, aryloxy carbonylalkyl, aralkoxycarbonyl,
- 30 aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl,

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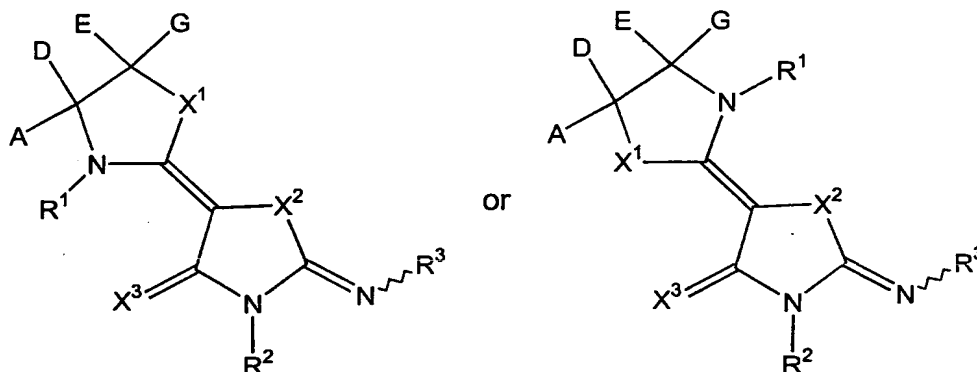
- arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, aralkoxycarbonyloxy,
- 5 aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, imino, hydroxyimino, alkoxyimino, aryloxyimino, aralkoxyimino, alkylazo, arylazo, aralkylazo, aminothiocarbonyl, alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl,
- 15 arylaminoalkyl, diarylaminoalkyl, alkylarylaminominoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylamino, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxycarbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxycarbonylamino, alkylsulfonylamino, arylsulfonylamino,
- 20 heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano, alkylsulfinyloxy,
- 25 alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl,
- 30 dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two  $Q^1$  groups, which substitute atoms in a 1,2 or



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- aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxy carbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxy carbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heterocyclylsulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  
**5**  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyno, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy,  
**10** alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two  $Q^2$  groups, which  
**15** substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy, thioalkylenoxy or alkylenedithioxy where y is 1 or 2; or two  $Q^2$  groups, which substitute the same atom, together form alkylene;  
 each  $Q^2$  is independently unsubstituted or substituted with one or more substituents each independently selected from alkyl, halo and pseudohalo;  
**20**  $R^{50}$  is hydroxy, alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or  $-NR^{70}R^{71}$ , where  $R^{70}$  and  $R^{71}$  are each independently hydrogen, alkyl, aralkyl, aryl, heteroaryl, heteroaralkyl or heterocyclyl, or  $R^{70}$  and  $R^{71}$  together form alkylene, azaalkylene, oxaalkylene or thiaalkylene;  
 $R^{51}$ ,  $R^{52}$  and  $R^{53}$  are each independently hydrogen, alkyl, aryl, aralkyl,  
**25** heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl;  
 $R^{60}$  is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl; and  
 $R^{63}$  is alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or  $-NR^{70}R^{71}$ .  
**62.** The compound of claim 1 that has formulae I:

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or a pharmaceutically acceptable derivative thereof, wherein:

X<sup>1</sup>, X<sup>2</sup> and X<sup>3</sup> are selected from (i) or (ii) as follows:

- (i) X<sup>1</sup>, X<sup>2</sup> and X<sup>3</sup> are each independently S, O or NR<sup>5</sup>; or
- 5 (ii) X<sup>1</sup> is -CR<sup>8</sup>=CR<sup>9</sup>-, where R<sup>8</sup> and R<sup>9</sup> are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl,
- 10 substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, halo, pseudohalo, OR<sup>10</sup>, NR<sup>14</sup>R<sup>15</sup> and C(=J)R<sup>13</sup>;; and X<sup>2</sup> and X<sup>3</sup> are each independently S, O or NR<sup>5</sup>;

- R<sup>1</sup> is substituted or unsubstituted alkyl, where there are 0 to 6
- 15 substituents selected from alkoxy, alkoxyalkyl, hydroxycarbonyl, alkylcarbonyloxy, hydroxy, halo, pseudohalo, aryl and heteroaryl;

- R<sup>2</sup> is substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
- 20 heteroaralkyl, or substituted or unsubstituted heterocyclylalkyl; where there are 0 or 1 substituents selected from alkoxycarbonyl and hydroxycarbonyl;

R<sup>3</sup> is substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl, or substituted or unsubstituted aralkyl; where there are 0 to 5 substituents selected from alkylamino, cyano, cycloalkyl, hydroxy, alkoxy,



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- dialkylamino, amino, heterocyclyl, aralkoxy, alkyl, nitro, haloalkyl, alkylcarbonyl, halo, alkylcarbonylamino, alkoxyalkylcarbonyl-amino, dialkylaminoalkylcarbonylamino, aminocarbonyl, alkoxycarbonyl, aralkylamino, cycloalkylamino, heterocyclylamino, haloalkylamino, haloalkoxy, 5 hydroxycarbonyl, aminosulfonyl, alkylcarbonylaminosulfonyl, or haloalkylcarbonylamino, or any two substituents, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy;

- A and G are each independently selected from hydrogen, substituted or unsubstituted aryl, substituted or unsubstituted alkyl, substituted or 10 unsubstituted alkoxy, hydroxycarbonyl, and substituted or unsubstituted alkylcarbonyl, where there are 0 to 5 substituents selected from aryl, haloalkyl, haloalkoxy, nitro, halo, pseudohalo, hydroxy, alkyl and alkoxy, or A and G together form substituted or unsubstituted alkylene, or substituted or unsubstituted azaalkylene, where there are 0 to 4 substituents selected 15 from halo, pseudohalo, alkoxy, nitro, haloalkyl, alkylcarbonylamino, hydroxy, alkylaminocarbonyloxy, alkoxy, aminocarbonylalkoxy, hydroxyalkoxy, alkyl, haloalkylaminocarbonyloxy and alkylaminoalkoxy;

D and E are each hydrogen, or together form a bond; and

- $R^5$  is hydrogen, substituted or unsubstituted alkyl, substituted or 20 unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, 25 halo, pseudohalo,  $OR^{10}$ ,  $SR^{10}$ ,  $S(=O)R^{13}$ ,  $S(=O)_2R^{13}$ ,  $NR^{14}R^{15}$  or  $C(=J)R^{13}$ ;

- $R^{10}$  is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclylalkyl, 30 substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,

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substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl or C(=J)R<sup>13</sup>;

J is O, S or NR<sup>14</sup>;

R<sup>13</sup> is selected from hydrogen, substituted or unsubstituted alkyl,

- 5 substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaralkyl, pseudohalo, OR<sup>16</sup> and NR<sup>14</sup>R<sup>15</sup>;

R<sup>14</sup>, R<sup>15</sup> and R<sup>16</sup> are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl;

wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl,

- 15 cycloalkylalkyl, heterocyclalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl moieties of R<sup>5</sup>, R<sup>10</sup> and R<sup>13</sup> are unsubstituted or substituted with one or more substituents each independently selected from Q<sup>1</sup>, where Q<sup>1</sup> is halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl, haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkylidiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl,
- 25 alkoxycarbonylalkyl, aryloxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy, perfluoroalkoxy, alkenyloxy, alkynyloxy,
- 30 aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, aralkoxycarbonyloxy,

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- aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylamino carbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido, N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-triarylureido, amidino, alkylamidino, arylamidino, imino, hydroxyimino, alkoxyimino, aralkoxyimino, arylazo, haloalkylcarbonylamino, aminothiocabonyl, alkylaminothiocabonyl, arylaminothiocabonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminominoalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylaminomino, alkylcarbonylamino, alkoxy carbonylamino, aralkoxy carbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl, aryloxy carbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxy carbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroaryl sulfonylamino, heterocyclyl sulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyno, isothiocyano, alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxy sulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylamino sulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxy sulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylamino sulfonyl or alkylarylaminosulfonyl; or two  $Q^1$  groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy, thioalkylenoxy or alkylenedithioxy; or two  $Q^1$  groups, which substitute the same atom, together form alkylene;

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each Q<sup>1</sup> is independently unsubstituted or substituted with one or more substituents each independently selected from Q<sup>2</sup>;

each Q<sup>2</sup> is independently halo, pseudohalo, hydroxy, oxo, thia, nitrile, nitro, formyl, mercapto, hydroxycarbonyl, hydroxycarbonylalkyl, alkyl,

- 5 haloalkyl, polyhaloalkyl, aminoalkyl, diaminoalkyl, alkenyl containing 1 to 2 double bonds, alkynyl containing 1 to 2 triple bonds, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, aralkyl, aralkenyl, aralkynyl, heteroarylalkyl, trialkylsilyl, dialkylarylsilyl, alkylidiarylsilyl, triarylsilyl, alkylidene, arylalkylidene, alkylcarbonyl, arylcarbonyl,
- 10 heteroarylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxy carbonyl, aryloxy carbonylalkyl, aralkoxycarbonyl, aralkoxycarbonylalkyl, arylcarbonylalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, arylalkylaminocarbonyl, alkoxy, aryloxy, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, cycloalkoxy,
- 15 perfluoroalkoxy, alkenyloxy, alkynyloxy, aralkoxy, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, aralkoxycarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylarylaminocarbonyloxy, diarylaminocarbonyloxy, guanidino, isothioureido, ureido, N-alkylureido, N-arylureido, N'-alkylureido,
- 20 N',N'-dialkylureido, N'-alkyl-N'-arylureido, N',N'-diarylureido, N'-arylureido, N,N'-dialkylureido, N-alkyl-N'-arylureido, N-aryl-N'-alkylureido, N,N'-diarylureido, N,N',N'-trialkylureido, N,N'-dialkyl-N'-arylureido, N-alkyl-N',N'-diarylureido, N-aryl-N',N'-dialkylureido, N,N'-diaryl-N'-alkylureido, N,N',N'-trialkylureido, amidino, alkylamidino, arylamidino, aminothiocarbonyl,
- 25 alkylaminothiocarbonyl, arylaminothiocarbonyl, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, diarylaminoalkyl, alkylarylaminalkyl, alkylamino, dialkylamino, haloalkylamino, arylamino, diarylamino, alkylarylaminalkyl, alkylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, arylcarbonylamino, arylcarbonylaminoalkyl,
- 30 aryloxy carbonylaminoalkyl, aryloxyarylcarbonylamino, aryloxy carbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino,

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- heterocyclisulfonylamino, heteroarylthio, azido,  $-N^+R^{51}R^{52}R^{53}$ ,  $P(R^{50})_2$ ,  $P(=O)(R^{50})_2$ ,  $OP(=O)(R^{50})_2$ ,  $-NR^{60}C(=O)R^{63}$ , dialkylphosphonyl, alkylarylphosphonyl, diarylphosphonyl, hydroxyphosphonyl, alkylthio, arylthio, perfluoroalkylthio, hydroxycarbonylalkylthio, thiocyano, isothiocyano,
- 5 alkylsulfinyloxy, alkylsulfonyloxy, arylsulfinyloxy, arylsulfonyloxy, hydroxysulfonyloxy, alkoxysulfonyloxy, aminosulfonyloxy, alkylaminosulfonyloxy, dialkylaminosulfonyloxy, arylaminosulfonyloxy, diarylaminosulfonyloxy, alkylarylaminosulfonyloxy, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, alkoxysulfonyl, aminosulfonyl,
- 10 alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, diarylaminosulfonyl or alkylarylaminosulfonyl; or two  $Q^2$  groups, which substitute atoms in a 1,2 or 1,3 arrangement, together form alkylenedioxy, thioalkylenoxy or alkylenedithioxy where y is 1 or 2; or two  $Q^2$  groups, which substitute the same atom, together form alkylene;
- 15  $R^{50}$  is hydroxy, alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or  $-NR^{70}R^{71}$ , where  $R^{70}$  and  $R^{71}$  are each independently hydrogen, alkyl, aralkyl, aryl, heteroaryl, heteroaralkyl or heterocyclyl, or  $R^{70}$  and  $R^{71}$  together form alkylene, azaalkylene, oxaalkylene or thiaalkylene;
- $R^{51}$ ,  $R^{52}$  and  $R^{53}$  are each independently hydrogen, alkyl, aryl, aralkyl,
- 20 heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl;
- $R^{60}$  is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl; and
- $R^{63}$  is alkoxy, aralkoxy, alkyl, heteroaryl, heterocyclyl, aryl or  $-NR^{70}R^{71}$ .

EXAMPLE	EC50_AVG	EFF_AVG	IC50_AVG	INHIB_AVG
1	D	C		
2	D	C		
3	D	C		
4	D	B		
5	C	B		
6	D	C		
7	D	D		
8	C	B		
9	C	B		
10	C	C		
11	B	B		
12	C	C		
13	C	B		
14	D	C		
15	C	C		
16	C	A		
17	C	C		
18	C	C		
19	C	D		
20	D	C		
21	C	B		
22	B	B		
23	C	C		
24	D	C		
25	D	C		
26	C	B		
27	C	B		

FIG. 1A

28	D	C		
29	C	B		
30	C	A		
31	B	B		
32	B	B		NEG
32	B	B		
32	A	B		
33	B	B		
34	C	C		
35	C	B		
36	B	A		
37	D	B		
38	A	A		
39	NC	NC		
40	NC	NC		
41	NC	NC		
42	NC	NC		
43	D	D		
44	D	D		
45	D	D		
46	NC	NC		
47	C	C	C	F
48	C	C	B	F
49	C	C	C	F
50	D	C		G
51	NC	D		
52	B	D	B	F
55	A	A		

FIG. 1B

56	A	A		
57	B	B		
58	B	D	A	F
59	B	C		
60	NC	NC	B	E
61	D	C		NEG
62	C	D		
63	C	C		
64	C	B		
65	C	C		
66	B	C		
67	C	A		
68	D	C		
69	C	C		
70	NC	NC		
71	C	B		
72	C	C		
73	C	B		
74	C	C		
75	D	C		
76	NC	NC		
77	NC	NC		
78	C	A		
79	C	B		
80	C	B		
81	B	B		
82	B	B		
82	B	B		

FIG. 1C



83	B	A		
84	B	B		
85	B	B		
86	C	B		
87	A	A		
88	NC	NC		
89	D	D		
90	B	B		
91	B	B		NEG
91	B	B		NEG
92	B	B		H
93	C	B		NEG
94	B	C		NEG
95	D	B		NEG
96	B	C	C	G
97	B	B		NEG
98	C	B		H
99	B	B		NEG
100	B	C		H
101	B	B		NEG
102	C	B		H
103	B	B	D	H
104	NC	NC		
105	C	C		
106	C	D		
107	NC	NC		
108	B	C		
109	C	C		

FIG. 1D

110	C	C	
112	NC	NC	
113	C	C	
114	C	B	
115	C	C	
116	D	B	
117	C	C	H
118	C	B	NEG
119	C	C	H
120	C	C	H
121	C	B	NEG
122	C	C	H
123	C	C	H
124	C	D	H
125	C	D	G
126	C	C	NEG
127	NC	NC	H
128	C	B	NEG
129	B	B	NEG
130	B	B	NEG
131	B	C	NEG
132	C	C	NEG
133	D	D	NEG
134	B	B	NEG
135	A	C	H
136	B	B	NEG
137	B	B	NEG
138	B	B	NEG

FIG. 1E

139	B	B		NEG
140	C	B		H
141	C	B		NEG
142	B	A		NEG
143	B	C		G
144	C	C	D	E
145	A	C	D	F
146	B	D	B	E
147	A	A		H
148	NC	D		G
149	B	D	C	E
150	A	B		
151	B	B		
152	A	B		G
153	B	B		
154	NC	NC	C	F
155	NC	NC		
156	NC	D		
157	B	B		
158	B	C		
159	B	D	A	F
160	C	D	B	F
161	B	D	B	F
162	B	C	B	F
163	B	D	A	F
164	B	D	B	F
165	C	D		G
166	NC	D		

FIG. 1F

167	C	C		
168	B	B		
169	C	B		
170	C	B		
171	C	A		
172	C	A		
173	C	A		
174	C	C		
175	C	B		
176	B	B		
177	NC	NC	B	E
178	D	C	C	G
179	B	A		
180	C	D		
181	D	C		
182	C	B		
183	C	D	D	G
184	C	B		NEG
185	C	C		H
186	B	B		NEG
187	NC	D		H
188	D	D	A	G
189	C	D	C	F
190	C	B		NEG
191	C	B		H
192	C	D	C	E
193	C	C	D	G
194	C	C		H

FIG. 1G

195	C	C		H
196	D	D	C	G
197	B	D	B	F
198	C	D	C	E
199	C	D	B	F
200	C	D	B	F
201	C	C		H
202	D	C		H
203	C	C		H
204	C	D	B	F
205	NC	D		NEG
206	B	A		NEG
207	C	C		NEG
208	C	B		NEG
209	C	B		NEG
210	C	B		NEG
211	B	B		NEG
212	C	C		H
213	D	D		H
214	C	D	C	G
215	C	D	C	F
216	C	D	B	E
217	B	D	B	F
218	B	D	B	E
219	B	C	B	G
220	C	D	B	E
221	B	D	B	F
222	D	D	D	E

FIG. 1H

223	B	D	B	G
224	C	D	C	F
225	C	C		G
227	B	C		
228	C	B		
229	B	C	B	G
230	D	B		
231	NC	NC	C	E
232	B	C		G
233	C	D		G
234	B	D	B	F
235	NC	NC		
236	D	C		
237	D	D		
238	D	D		
239	NC	NC		
240	NC	NC		
241	NC	D		
241	NC	NC		
242	C	D		
242	NC	NC		
243	B	B		
244	C	A		
244	A	A		
245	B	C		
246	NC	D		
247	C	C		
248	B	D	C	E

FIG. 1I

248	B	D	C	E
249	C	C	A	G
250	B	C		
251	C	C		
252	NC	D		
253	D	D		
254	C	D		
255	B	D	A	E
256	D	D		
257	NC	NC	C	F
258	C	D	C	F
259	NC	NC	C	F
259	NC	NC	C	F
259	C	D	B	E
260	NC	NC	B	G
261	B	D	B	G
262	B	C	A	H
263	C	D	B	F
264	B	D	A	F
265	B	B		
266	C	B		
267	B	B		
268	B	D	A	G
269	B	C		
270	B	B		H
271	B	D	B	F
272	B	B		NEG
273	D	C		H

FIG. 1J

274	B	D	B	E
275	A	D		NEG
276	B	C		NEG
277	C	D		G
278	NC	NC		G
279	C	D	C	F
280	C	D	C	G
281	C	D		NEG
282	C	D	C	E
283	NC	NC	C	E
284	NC	NC		H
285	NC	C	A	G
286	B	C	A	G
287	C	D	B	G
288	C	D	C	G
289	C	D		H
290	B	C		NEG

FIG. 1K



- 1 -

## SEQUENCE LISTING

&lt;110&gt; X-Cepto Therapeutics, Inc.

Martin Richard  
 Flatt Brenton Todd  
 Kahl Jeffrey Dean  
 Wang Tie-Lin

&lt;120&gt; HETEROCYCLIC MODULATORS OF NUCLEAR RECEPTORS

&lt;130&gt; 38205-3001PC

&lt;140&gt; Unassigned

&lt;141&gt; Herewith

&lt;150&gt; 60/342,720

&lt;151&gt; 2001-12-21

&lt;160&gt; 18

&lt;170&gt; FastSEQ for Windows Version 4.0

&lt;210&gt; 1

&lt;211&gt; 1528

&lt;212&gt; DNA

&lt;213&gt; Homo Sapien

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (36)...(1379)

&lt;300&gt;

&lt;308&gt; GeneBank NM\_005693

&lt;309&gt; 2002-05-14

&lt;400&gt; 1

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          Met Ser Leu Trp Leu Gly
                      1          5

gcc cct gtg cct gac att cct cct gac tct gcg gtg gag ctg tgg aag 101
Ala Pro Val Pro Asp Ile Pro Pro Asp Ser Ala Val Glu Leu Trp Lys
          10          15          20

cca ggc gca cag gat gca agc agc cag gcc cag gga ggc agc agc tgc 149
Pro Gly Ala Gln Asp Ala Ser Ser Gln Ala Gln Gly Gly Ser Ser Cys
          25          30          35

atc ctc aga gag gaa gcc agg atg ccc cac tct gct ggg ggt act gca 197
Ile Leu Arg Glu Glu Ala Arg Met Pro His Ser Ala Gly Gly Thr Ala
          40          45          50

ggg gtg ggg ctg gag gct gca gag ccc aca gcc ctg ctc acc agg gca 245
Gly Val Gly Leu Glu Ala Ala Glu Pro Thr Ala Leu Leu Thr Arg Ala
          55          60          65          70

gag ccc cct tca gaa ccc aca gag atc cgt cca caa aag cgg aaa aag 293
Glu Pro Pro Ser Glu Pro Thr Glu Ile Arg Pro Gln Lys Arg Lys Lys
          75          80          85

ggg cca gcc ccc aaa atg ctg ggg aac gag cta tgc agc gtg tgt ggg 341
Gly Pro Ala Pro Lys Met Leu Gly Asn Glu Leu Cys Ser Val Cys Gly
          90          95          100

gac aag gcc tcg ggc ttc cac tac aat gtt ctg agc tgc gag ggc tgc 389

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Asp	Lys	Ala	Ser	Gly	Phe	His	Tyr	Asn	Val	Leu	Ser	Cys	Glu	Gly	Cys	
		105					110					115				
aag	gga	ttc	ttc	cgc	cgc	agc	gtc	atc	aag	gga	gcg	cac	tac	atc	tgc	437
Lys	Gly	Phe	Phe	Arg	Arg	Ser	Val	Ile	Lys	Gly	Ala	His	Tyr	Ile	Cys	
	120					125					130					
cac	agt	ggc	ggc	cac	tgc	ccc	atg	gac	acc	tac	atg	cgt	cgc	aag	tgc	485
His	Ser	Gly	Gly	His	Cys	Pro	Met	Asp	Thr	Tyr	Met	Arg	Arg	Lys	Cys	
135					140					145					150	
cag	gag	tgt	cgg	ctt	cgc	aaa	tgc	cgt	cag	gct	ggc	atg	cgg	gag	gag	533
Gln	Glu	Cys	Arg	Leu	Arg	Lys	Cys	Arg	Gln	Ala	Gly	Met	Arg	Glu	Glu	
				155					160					165		
tgt	gtc	ctg	tca	gaa	gaa	cag	atc	cgc	ctg	aag	aaa	ctg	aag	cgg	caa	581
Cys	Val	Leu	Ser	Glu	Glu	Gln	Ile	cgc	Leu	Lys	Lys	Leu	Lys	Arg	Gln	
			170					175					180			
gag	gag	gaa	cag	gct	cat	gcc	aca	tcc	ttg	ccc	ccc	agg	cgt	tcc	tca	629
Glu	Glu	Glu	Gln	Ala	His	Ala	Thr	Ser	Leu	Pro	Pro	Arg	Arg	Ser	Ser	
		185				190						195				
ccc	ccc	caa	atc	ctg	ccc	cag	ctc	agc	ccg	gaa	caa	ctg	ggc	atg	atc	677
Pro	Pro	Gln	Ile	Leu	Pro	Gln	Leu	Ser	Pro	Glu	Gln	Leu	Gly	Met	Ile	
	200					205					210					
gag	aag	ctc	gtc	gct	gcc	cag	caa	cag	tgt	aac	cgg	cgc	tcc	ttt	tct	725
Glu	Lys	Leu	Val	Ala	Ala	Gln	Gln	Gln	Cys	Asn	Arg	Arg	Ser	Phe	Ser	
215					220				225					230		
gac	cgg	ctt	cga	gtc	acg	cct	tgg	ccc	atg	gca	cca	gat	ccc	cat	agc	773
Asp	Arg	Leu	Arg	Val	Thr	Pro	Trp	Pro	Met	Ala	Pro	Asp	Pro	His	Ser	
				235				240						245		
cgg	gag	gcc	cgt	cag	cag	cgc	ttt	gcc	cac	ttc	act	gag	ctg	gcc	atc	821
Arg	Glu	Ala	Arg	Gln	Gln	Arg	Phe	Ala	His	Phe	Thr	Glu	Leu	Ala	Ile	
		250						255					260			
gtc	tct	gtg	cag	gag	ata	gtt	gac	ttt	gct	aaa	cag	cta	ccc	ggc	ttc	869
Val	Ser	Val	Gln	Glu	Ile	Val	Asp	Phe	Ala	Lys	Gln	Leu	Pro	Gly	Phe	
		265				270						275				
ctg	cag	ctc	agc	cgg	gag	gac	cag	att	gcc	ctg	ctg	aag	acc	tct	gcg	917
Leu	Gln	Leu	Ser	Arg	Glu	Asp	Gln	Ile	Ala	Leu	Leu	Lys	Thr	Ser	Ala	
		280				285					290					
atc	gag	gtg	atg	ctt	ctg	gag	aca	tct	cgg	agg	tac	aac	cct	ggg	agt	965
Ile	Glu	Val	Met	Leu	Leu	Glu	Thr	Ser	Arg	Arg	Tyr	Asn	Pro	Gly	Ser	
295					300				305					310		
gag	agt	atc	acc	ttc	ctc	aag	gat	ttc	agt	tat	aac	cgg	gaa	gac	ttt	1013
Glu	Ser	Ile	Thr	Phe	Leu	Lys	Asp	Phe	Ser	Tyr	Asn	Arg	Glu	Asp	Phe	
				315				320						325		
gcc	aaa	gca	ggg	ctg	caa	gtg	gaa	ttc	atc	aac	ccc	atc	ttc	gag	ttc	1061
Ala	Lys	Ala	Gly	Leu	Gln	Val	Glu	Phe	Ile	Asn	Pro	Ile	Phe	Glu	Phe	
			330					335					340			
tcc	agg	gcc	atg	aat	gag	ctg	caa	ctc	aat	gat	gcc	gag	ttt	gcc	ttg	1109
Ser	Arg	Ala	Met	Asn	Glu	Leu	Gln	Leu	Asn	Asp	Ala	Glu	Phe	Ala	Leu	
			345				350					355				
ctc	att	gct	atc	agc	atc	ttc	tct	gca	gac	cgg	ccc	aac	gtg	cag	gac	1157
Leu	Ile	Ala	Ile	Ser	Ile	Phe	Ser	Ala	Asp	Arg	Pro	Asn	Val	Gln	Asp	
		360				365					370					

- 3 -

```

cag ctc cag gtg gag agg ctg cag cac aca tat gtg gaa gcc ctg cat 1205
Gln Leu Gln Val Glu Arg Leu Gln His Thr Tyr Val Glu Ala Leu His 390
375 380 385

gcc tac gtc tcc atc cac cat ccc cat gac cga ctg atg ttc cca cgg 1253
Ala Tyr Val Ser Ile His His Pro His Asp Arg Leu Met Phe Pro Arg 405
395 400

atg cta atg aaa ctg gtg agc ctc cgg acc ctg agc agc gtc cac tca 1301
Met Leu Met Lys Leu Val Ser Leu Arg Thr Leu Ser Ser Val His Ser 420
410 415

gag caa gtg ttt gca ctg cgt ctg cag gac aaa aag ctc cca ccg ctg 1349
Glu Gln Val Phe Ala Leu Arg Leu Gln Asp Lys Lys Leu Pro Pro Leu 435
425 430

ctc tct gag atc tgg gat gtg cac gaa tga ctgttctgtc cccatatttt 1399
Leu Ser Glu Ile Trp Asp Val His Glu * 440 445

ctgttttctt ggccggatgg ctgaggcctg gtggctgcct cctagaagtg gaacagactg 1459
agaagggcaa acattcctgg gagctgggca aggagatcct cccgtggcat taaaagagag 1519
tcaaagggt 1528

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&lt;210&gt; 2

&lt;211&gt; 447

&lt;212&gt; PRT

&lt;213&gt; Homo Sapien

&lt;400&gt; 2

```

Met Ser Leu Trp Leu Gly Ala Pro Val Pro Asp Ile Pro Pro Asp Ser
1 5 10 15
Ala Val Glu Leu Trp Lys Pro Gly Ala Gln Asp Ala Ser Ser Gln Ala
20 25 30
Gln Gly Gly Ser Ser Cys Ile Leu Arg Glu Glu Ala Arg Met Pro His
35 40 45
Ser Ala Gly Gly Thr Ala Gly Val Gly Leu Glu Ala Ala Glu Pro Thr
50 55 60
Ala Leu Leu Thr Arg Ala Glu Pro Pro Ser Glu Pro Thr Glu Ile Arg
65 70 75 80
Pro Gln Lys Arg Lys Lys Gly Pro Ala Pro Lys Met Leu Gly Asn Glu
85 90 95
Leu Cys Ser Val Cys Gly Asp Lys Ala Ser Gly Phe His Tyr Asn Val
100 105 110
Leu Ser Cys Glu Gly Cys Lys Gly Phe Phe Arg Arg Ser Val Ile Lys
115 120 125
Gly Ala His Tyr Ile Cys His Ser Gly Gly His Cys Pro Met Asp Thr
130 135 140
Tyr Met Arg Arg Lys Cys Gln Glu Cys Arg Leu Arg Lys Cys Arg Gln
145 150 155 160
Ala Gly Met Arg Glu Glu Cys Val Leu Ser Glu Glu Gln Ile Arg Leu
165 170 175
Lys Lys Leu Lys Arg Gln Glu Glu Glu Gln Ala His Ala Thr Ser Leu
180 185 190
Pro Pro Arg Arg Ser Ser Pro Pro Gln Ile Leu Pro Gln Leu Ser Pro
195 200 205
Glu Gln Leu Gly Met Ile Glu Lys Leu Val Ala Ala Gln Gln Gln Cys
210 215 220
Asn Arg Arg Ser Phe Ser Asp Arg Leu Arg Val Thr Pro Trp Pro Met
225 230 235 240
Ala Pro Asp Pro His Ser Arg Glu Ala Arg Gln Gln Arg Phe Ala His
245 250 255
Phe Thr Glu Leu Ala Ile Val Ser Val Gln Glu Ile Val Asp Phe Ala
260 265 270
Lys Gln Leu Pro Gly Phe Leu Gln Leu Ser Arg Glu Asp Gln Ile Ala
275 280 285
Leu Leu Lys Thr Ser Ala Ile Glu Val Met Leu Leu Glu Thr Ser Arg

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Arg	Tyr	Asn	Pro	Gly	Ser	Glu	Ser	Ile	Thr	Phe	Leu	Lys	Asp	Phe	Ser
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Tyr	Asn	Arg	Glu	Asp	Phe	Ala	Lys	Ala	Gly	Leu	Gln	Val	Glu	Phe	Ile
				325					330					335	
Asn	Pro	Ile	Phe	Glu	Phe	Ser	Arg	Ala	Met	Asn	Glu	Leu	Gln	Leu	Asn
				340					345					350	
Asp	Ala	Glu	Phe	Ala	Leu	Leu	Ile	Ala	Ile	Ser	Ile	Phe	Ser	Ala	Asp
				355					360				365		
Arg	Pro	Asn	Val	Gln	Asp	Gln	Leu	Gln	Val	Glu	Arg	Leu	Gln	His	Thr
						375					380				
Tyr	Val	Glu	Ala	Leu	His	Ala	Tyr	Val	Ser	Ile	His	His	Pro	His	Asp
					390					395					400
Arg	Leu	Met	Phe	Pro	Arg	Met	Leu	Met	Lys	Leu	Val	Ser	Leu	Arg	Thr
				405					410					415	
Leu	Ser	Ser	Val	His	Ser	Glu	Gln	Val	Phe	Ala	Leu	Arg	Leu	Gln	Asp
				420					425					430	
Lys	Lys	Leu	Pro	Pro	Leu	Leu	Ser	Glu	Ile	Trp	Asp	Val	His	Glu	
				435			440					445			

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<210> 3
<211> 1815
<212> DNA
<213> Homo Sapien
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<220>
<221> CDS
<222> (56) ... (1438)
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<300>  
<308> GeneBank XM\_046419  
<309> 2002-08-01

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						Met											
						1											
tcc	tct	cct	acc	acg	agt	tcc	ctg	gat	acc	ccc	ctg	cct	gga	aat	ggc		106
Ser	Ser	Pro	Thr	Thr	Ser	Ser	Leu	Asp	Thr	Pro	Leu	Pro	Gly	Asn	Gly		
			5					10					15				
ccc	cct	cag	cct	ggc	gcc	cct	tct	tct	tca	ccc	act	gta	aag	gag	gag		154
Pro	Pro	Gln	Pro	Gly	Ala	Pro	Ser	Ser	Ser	Pro	Thr	Val	Lys	Glu	Glu		
			20				25					30					
ggt	ccg	gag	ccg	tgg	ccc	ggg	ggt	ccg	gac	cct	gat	gtc	cca	ggc	act		202
Gly	Pro	Glu	Pro	Trp	Pro	Gly	Gly	Pro	Asp	Pro	Asp	Val	Pro	Gly	Thr		
	35					40					45						
gat	gag	gcc	agc	tca	gcc	tgc	agc	aca	gac	tgg	gtc	atc	cca	gat	ccc		250
Asp	Glu	Ala	Ser	Ser	Ala	Cys	Ser	Thr	Asp	Trp	Val	Ile	Pro	Asp	Pro		
					55					60					65		
gaa	gag	gaa	cca	gag	cgc	aag	cga	aag	aag	ggc	cca	gcc	ccg	aag	atg		298
Glu	Glu	Glu	Pro	Glu	Arg	Lys	Arg	Lys	Lys	Gly	Pro	Ala	Pro	Lys	Met		
				70					75					80			
ctg	ggc	cac	gag	ctt	tgc	cgt	gtc	tgt	ggg	gac	aag	gcc	tcc	ggc	ttc		346
Leu	Gly	His	Glu	Leu	Cys	Arg	Val	Cys	Gly	Asp	Lys	Ala	Ser	Gly	Phe		
			85					90					95				
cac	tac	aac	gtg	ctc	agc	tgc	gaa	ggc	tgc	aag	ggc	ttc	ttc	cgg	cgc		394
His	Tyr	Asn	Val	Leu	Ser	Cys	Glu	Gly	Cys	Lys	Gly	Phe	Phe	Arg	Arg		
		100					105					110					

-5-

agt Ser	gtg Val	gtc Val	cgt Arg	ggg Gly	ggg Gly	gcc Ala	agg Arg	cgc Arg	tat Tyr	gcc Ala	tgc Cys	cgg Arg	ggt Gly	ggc Gly	gga Gly	442
115						120					125					
acc Thr	tgc Cys	cag Gln	atg Met	gac Asp	gct Ala	ttc Phe	atg Met	cgg Arg	cgc Arg	aag Lys	tgc Cys	cag Gln	cag Gln	tgc Cys	cgg Arg	490
130					135					140					145	
ctg Leu	cgc Arg	aag Lys	tgc Cys	aag Lys	gag Glu	gca Ala	ggg Gly	atg Met	agg Arg	gag Glu	cag Gln	tgc Cys	gtc Val	ctt Leu	tct Ser	538
				150					155					160		
gaa Glu	gaa Glu	cag Gln	atc Ile	cgg Arg	aag Lys	aag Lys	aag Lys	att Ile	cgg Arg	aaa Lys	cag Gln	cag Gln	cag Gln	gag Glu	tca Ser	586
			165					170					175			
cag Gln	tca Ser	cag Gln	tcg Ser	cag Gln	tca Ser	cct Pro	gtg Val	ggg Gly	ccg Pro	cag Gln	ggc Gly	agc Ser	agc Ser	agc Ser	tca Ser	634
			180				185					190				
gcc Ala	tct Ser	ggg Gly	cct Pro	ggg Gly	gct Ala	tcc Ser	cct Pro	ggg Gly	gga Gly	tct Ser	gag Glu	gca Ala	ggc Gly	agc Ser	cag Gln	682
195						200					205					
ggc Gly	tcc Ser	ggg Gly	gaa Glu	ggc Gly	gag Glu	ggg Gly	gtc Val	cag Gln	cta Leu	aca Ala	gcg Ala	gct Ala	caa Gln	gaa Glu	cta Leu	730
210					215					220					225	
atg Met	atc Ile	cag Gln	cag Gln	ttg Leu	gtg Val	ggg Ala	gcc Ala	caa Gln	ctg Leu	cag Gln	tgc Cys	aac Asn	aaa Lys	cgc Arg	tcc Ser	778
				230					235					240		
ttc Phe	tcc Ser	gac Asp	cag Gln	ccc Pro	aaa Lys	gtc Val	acg Thr	ccc Pro	tgg Trp	ccc Pro	ctg Leu	ggc Gly	gca Ala	gac Asp	ccc Pro	826
			245					250					255			
cag Gln	tcc Ser	cga Arg	gat Asp	gcc Ala	cgc Arg	cag Gln	caa Gln	cgc Arg	ttt Phe	gcc Ala	cac His	ttc Phe	acg Thr	gag Glu	ctg Leu	874
		260					265					270				
gcc Ala	atc Ile	atc Ile	tca Ser	gtc Val	cag Gln	gag Glu	atc Ile	gtg Val	gac Asp	ttc Phe	gct Ala	aag Lys	caa Gln	gtg Val	cct Pro	922
275						280					285					
ggg Gly	ttc Phe	ctg Leu	cag Gln	ctg Leu	ggc Gly	cgg Arg	gag Glu	gac Asp	cag Gln	atc Ile	gcc Ala	ctc Leu	ctg Leu	aag Lys	gca Ala	970
290					295					300					305	
tcc Ser	act Thr	atc Ile	gag Glu	atc Ile	atg Met	ctg Leu	cta Leu	gag Glu	aca Thr	gcc Ala	agg Arg	cgc Arg	tac Tyr	aac Asn	cac His	1018
				310					315					320		
gag Glu	aca Thr	gag Glu	tgt Cys	atc Ile	acc Thr	ttc Phe	ttg Leu	aag Lys	gac Asp	ttc Phe	acc Thr	tac Tyr	agc Ser	aag Lys	gac Asp	1066
			325					330					335			
gac Asp	ttc Phe	cac His	cgt Arg	gca Ala	ggc Gly	ctg Leu	cag Gln	gtg Val	gag Glu	ttc Phe	atc Ile	aac Asn	ccc Pro	atc Ile	ttc Phe	1114
		340					345					350				
gag Glu	ttc Phe	tcg Ser	cgg Arg	gcc Ala	atg Met	cgg Arg	cgg Arg	ctg Leu	ggc Gly	ctg Leu	gac Asp	gac Asp	gct Ala	gag Glu	tac Tyr	1162
		355				360					365					
gcc Ala	ctg Leu	ctc Leu	atc Ile	gcc Ala	atc Ile	aac Asn	atc Ile	ttc Phe	tcg Ser	gcc Ala	gac Asp	cgg Arg	ccc Pro	aac Asn	gtg Val	1210
370					375					380					385	

- 6 -

cag gag ccg ggc cgc gtg gag gcg ttg cag cag ccc tac gtg gag gcg 1258  
 Gln Glu Pro Gly Arg Val Glu Ala Leu Gln Gln Pro Tyr Val Glu Ala  
 390 395 400  
 ctg ctg tcc tac acg cgc atc aag agg ccg cag gac cag ctg cgc ttc 1306  
 Leu Leu Ser Tyr Thr Arg Ile Lys Arg Pro Gln Asp Gln Leu Arg Phe  
 405 410 415  
 ccg cgc atg ctc atg aag ctg gtg agc ctg cgc acg ctg agc tct gtg 1354  
 Pro Arg Met Leu Met Lys Leu Val Ser Leu Arg Thr Leu Ser Ser Val  
 420 425 430  
 cac tcg gag cag gtc ttc gcc ttg cgg ctc cag gac aag aag ctg ccg 1402  
 His Ser Glu Gln Val Phe Ala Leu Arg Leu Gln Asp Lys Lys Leu Pro  
 435 440 445  
 cct ctg ctg tcg gag atc tgg gac gtc cac gag tga ggggctggcc 1448  
 Pro Leu Leu Ser Glu Ile Trp Asp Val His Glu \*  
 450 455 460  
 acccagcccc acagccttgc ctgaccaccc tccagcagat agacgccggc accccttccct 1508  
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 cccccctagc ccgggagacc agggccttcc tcttctctcg cttttattta ataaaaaacta 1808  
 aaaacag 1815

&lt;210&gt; 4

&lt;211&gt; 460

&lt;212&gt; PRT

&lt;213&gt; Homo Sapien

&lt;400&gt; 4

Met Ser Ser Pro Thr Thr Ser Ser Leu Asp Thr Pro Leu Pro Gly Asn  
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 Gly Pro Pro Gln Pro Gly Ala Pro Ser Ser Pro Thr Val Lys Glu  
 20 25 30  
 Glu Gly Pro Glu Pro Trp Pro Gly Gly Pro Asp Pro Asp Val Pro Gly  
 35 40 45  
 Thr Asp Glu Ala Ser Ser Ala Cys Ser Thr Asp Trp Val Ile Pro Asp  
 50 55 60  
 Pro Glu Glu Glu Pro Glu Arg Lys Arg Lys Lys Gly Pro Ala Pro Lys  
 65 70 75 80  
 Met Leu Gly His Glu Leu Cys Arg Val Cys Gly Asp Lys Ala Ser Gly  
 85 90 95  
 Phe His Tyr Asn Val Leu Ser Cys Glu Gly Cys Lys Gly Phe Phe Arg  
 100 105 110  
 Arg Ser Val Val Arg Gly Gly Ala Arg Arg Tyr Ala Cys Arg Gly Gly  
 115 120 125  
 Gly Thr Cys Gln Met Asp Ala Phe Met Arg Arg Lys Cys Gln Gln Cys  
 130 135 140  
 Arg Leu Arg Lys Cys Lys Glu Ala Gly Met Arg Glu Gln Cys Val Leu  
 145 150 155 160  
 Ser Glu Glu Gln Ile Arg Lys Lys Lys Ile Arg Lys Gln Gln Gln Glu  
 165 170 175  
 Ser Gln Ser Gln Ser Gln Ser Pro Val Gly Pro Gln Gly Ser Ser Ser  
 180 185 190  
 Ser Ala Ser Gly Pro Gly Ala Ser Pro Gly Gly Ser Glu Ala Gly Ser  
 195 200 205  
 Gln Gly Ser Gly Glu Gly Glu Gly Val Gln Leu Thr Ala Ala Gln Glu  
 210 215 220  
 Leu Met Ile Gln Gln Leu Val Ala Ala Gln Leu Gln Cys Asn Lys Arg  
 225 230 235 240  
 Ser Phe Ser Asp Gln Pro Lys Val Thr Pro Trp Pro Leu Gly Ala Asp  
 245 250 255

-7-

Pro Gln Ser Arg Asp Ala Arg Gln Gln Arg Phe Ala His Phe Thr Glu  
 260 265 270  
 Leu Ala Ile Ile Ser Val Gln Glu Ile Val Asp Phe Ala Lys Gln Val  
 275 280 285  
 Pro Gly Phe Leu Gln Leu Gly Arg Glu Asp Gln Ile Ala Leu Leu Lys  
 290 295 300  
 Ala Ser Thr Ile Glu Ile Met Leu Leu Glu Thr Ala Arg Arg Tyr Asn  
 305 310 315 320  
 His Glu Thr Glu Cys Ile Thr Phe Leu Lys Asp Phe Thr Tyr Ser Lys  
 325 330 335  
 Asp Asp Phe His Arg Ala Gly Leu Gln Val Glu Phe Ile Asn Pro Ile  
 340 345 350  
 Phe Glu Phe Ser Arg Ala Met Arg Arg Leu Gly Leu Asp Asp Ala Glu  
 355 360 365  
 Tyr Ala Leu Leu Ile Ala Ile Asn Ile Phe Ser Ala Asp Arg Pro Asn  
 370 375 380  
 Val Gln Glu Pro Gly Arg Val Glu Ala Leu Gln Gln Pro Tyr Val Glu  
 385 390 395 400  
 Ala Leu Leu Ser Tyr Thr Arg Ile Lys Arg Pro Gln Asp Gln Leu Arg  
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 Gln Asn Leu Asp Leu Glu Ser Tyr Ser Pro Tyr Asn Asn Val Gln Phe  
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 Pro Gln Val Gln Pro Gln Ile Ser Ser Ser Ser Tyr Tyr Ser Asn Leu  
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 Gly Phe Tyr Pro Gln Gln Pro Glu Asp Trp Tyr Ser Pro Gly Leu Tyr  
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Val Ser Glu Met Pro Val Thr Lys Lys Pro Arg Met Ala Ala Ser Ser	
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Ala Gly Arg Ile Lys Gly Asp Glu Leu Cys Val Val Cys Gly Asp Arg	
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Ala Ser Gly Tyr His Tyr Asn Ala Leu Thr Cys Glu Gly Cys Lys Gly	
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Arg Gln Val Thr Ser Thr Lys Leu Cys Arg Glu Lys Thr Glu Leu	
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Thr Val Asp Gln Gln Thr Leu Leu Asp Tyr Ile Met Asp Ser Tyr Ser	
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Ile Leu Ser Pro Asp Arg Gln Tyr Ile Lys Asp Arg Glu Ala Val Glu			
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Trp Arg Val Asn Asp His Lys Phe Thr Pro Leu Leu Cys Glu Ile Trp			
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Asp Val Gln *			

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Thr Glu Val Ser Glu Met Pro Val Thr Lys Lys Pro Arg Met Ala Ala	
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 Cys Leu Leu Thr Glu Ile Gln Cys Lys Ser Lys Arg Leu Arg Lys Asn  
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 Val Lys Gln His Ala Asp Gln Thr Val Asn Glu Asp Ser Glu Gly Arg  
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 Asp Leu Arg Gln Val Thr Ser Thr Thr Lys Leu Cys Arg Glu Lys Thr  
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 Glu Leu Thr Val Asp Gln Gln Thr Leu Leu Asp Tyr Ile Met Asp Ser  
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 Tyr Ser Lys Gln Arg Met Pro Gln Glu Ile Thr Asn Lys Ile Leu Lys  
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 Phe Gln Thr Leu Asp His Glu Asp Gln Ile Ala Leu Leu Lys Gly Ser  
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85 90 95	
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165 170 175	
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Thr Ala Ile Val Ile Leu Ser Pro Asp Arg Gln Tyr Ile Lys Asp Arg
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450 455 460 465

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 Leu His Ser Pro Ile Ser Thr Leu Ser Ser Pro Ile Asn Gly Met Gly  
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cgc tac cag aag tgc ctg gcc atg ggc atg aag cgg gaa gcc gtg cag 686  
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gag gag cgg cag cgt ggc aag gac cgg aac gag aat gag gtg gag tcg 734  
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acc agc agc gcc aac gag gac atg ccg gtg gag agg atc ctg gag gct 782



-16-

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Phe Ser Val Ile Ser Ser Pro Met Gly Pro His Ser Met Ser Val Pro  
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Pro Met Asn Pro Val Ser Ser Ser Glu Asp Ile Lys Pro Pro Leu Gly  
100 105 110  
Leu Asn Gly Val Leu Lys Val Pro Ala His Pro Ser Gly Asn Met Ala  
115 120 125  
Ser Phe Thr Lys His Ile Cys Ala Ile Cys Gly Asp Arg Ser Ser Gly  
130 135 140  
Lys His Tyr Gly Val Tyr Ser Cys Glu Gly Cys Lys Gly Phe Phe Lys  
145 150 155 160  
Arg Thr Val Arg Lys Asp Leu Thr Tyr Thr Cys Arg Asp Asn Lys Asp  
165 170 175  
Cys Leu Ile Asp Lys Arg Gln Arg Asn Arg Cys Gln Tyr Cys Arg Tyr  
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Gln Lys Cys Leu Ala Met Gly Met Lys Arg Glu Ala Val Gln Glu Glu  
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Arg Gln Arg Gly Lys Asp Arg Asn Glu Asn Glu Val Glu Ser Thr Ser  
210 215 220  
Ser Ala Asn Glu Asp Met Pro Val Glu Arg Ile Leu Glu Ala Glu Leu  
225 230 235 240  
Ala Val Glu Pro Lys Thr Glu Thr Tyr Val Glu Ala Asn Met Gly Leu  
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260 265 270  
Asp Lys Gln Leu Phe Thr Leu Val Glu Trp Ala Lys Arg Ile Pro His  
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Trp Asn Glu Leu Leu Ile Ala Ser Phe Ser His Arg Ser Ile Ala Val  
305 310 315 320  
Lys Asp Gly Ile Leu Leu Ala Thr Gly Leu His Val His Arg Asn Ser  
325 330 335  
Ala His Ser Ala Gly Val Gly Ala Ile Phe Asp Arg Val Leu Thr Glu  
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Leu Val Ser Lys Met Arg Asp Met Gln Met Asp Lys Thr Glu Leu Gly  
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&lt;222&gt; (167) ... (1573)

&lt;300&gt;

&lt;308&gt; GeneBank X57638

&lt;309&gt; 1991-03-19

&lt;400&gt; 11

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aca gag agc ccc atc tgt cct ctc tcc cca ctg gag gca gat gac ctg 223
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gaa agt ccc tta tct gaa gaa ttc tta caa gaa atg gga aac att caa 271
Glu Ser Pro Leu Ser Glu Glu Phe Leu Gln Glu Met Gly Asn Ile Gln
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gag att tct cag tcc atc ggt gag gag agc tct gga agc ttt ggt ttt 319
Glu Ile Ser Gln Ser Ile Gly Glu Glu Ser Ser Gly Ser Phe Gly Phe
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ccc gtg atc ccc gcc agc acg gac gag tcc ccc ggc agt gcc ctg aac 463
Pro Val Ile Pro Ala Ser Thr Asp Glu Ser Pro Gly Ser Ala Leu Asn
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Ile Glu Cys Arg Ile Cys Gly Asp Lys Ala Ser Gly Tyr His Tyr Gly
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Val His Ala Cys Glu Gly Cys Lys Gly Phe Phe Arg Arg Thr Ile Arg
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ctg aag ctg gtg tac gac aag tgt gat cgg agc tgc aag att cag aag 607
Leu Lys Leu Val Tyr Asp Lys Cys Asp Arg Ser Cys Lys Ile Gln Lys
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aag aac cgg aac aaa tgc cag tac tgc cgt ttt cac aag tgc ctg tct 655
Lys Asn Arg Asn Lys Cys Gln Tyr Cys Arg Phe His Lys Cys Leu Ser
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gaa aaa gca aaa ctg aaa gca gaa att ctt acc tgt gaa cac gac ctg 751
Glu Lys Ala Lys Leu Lys Ala Glu Ile Leu Thr Cys Glu His Asp Leu
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aaa gat tcg gaa act gca gac ctc aaa tct ctg ggc aag aga atc cac 799
Lys Asp Ser Glu Thr Ala Asp Leu Lys Ser Leu Gly Lys Arg Ile His
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Ile	Leu	Ala	Gly	Lys	Thr	Ser	Asn	Asn	Pro	Pro	Phe	Val	Ile	His	Asp	
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Met	Glu	Thr	Leu	Cys	Met	Ala	Glu	Lys	Thr	Leu	Val	Ala	Lys	Met	Val	
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gcc	aac	ggc	gtc	gaa	gac	aaa	gag	gca	gag	gtc	cga	ttc	ttc	cac	tgc	991
Ala	Asn	Gly	Val	Glu	Asp	Lys	Glu	Ala	Glu	Val	Arg	Phe	Phe	His	Cys	
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Lys	Ala	Ile	Pro	Gly	Phe	Ala	Asn	Leu	Asp	Leu	Asn	Asp	Gln	Val	Thr	
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Asp	Ser	Asp	Ile	Ser	Leu	Phe	Val	Ala	Ala	Ile	Ile	Cys	Cys	Gly	Asp	
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Ser	Asp	Ala	Ala	Leu	His	Pro	Leu	Leu	Gln	Glu	Ile	Tyr	Arg	Asp	Met	
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Tyr	*															

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&lt;210&gt; 12

&lt;211&gt; 468

&lt;212&gt; PRT

&lt;213&gt; Mus musculus

&lt;400&gt; 12

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50      55      60
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65      70      75      80
Val Ser Cys Pro Val Ile Pro Ala Ser Thr Asp Glu Ser Pro Gly Ser
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His Tyr Gly Val His Ala Cys Glu Gly Cys Lys Gly Phe Phe Arg Arg
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Thr Ile Arg Leu Lys Leu Val Tyr Asp Lys Cys Asp Arg Ser Cys Lys
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Pro Arg Ser Glu Lys Ala Lys Leu Lys Ala Glu Ile Leu Thr Cys Glu
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His Asp Leu Lys Asp Ser Glu Thr Ala Asp Leu Lys Ser Leu Gly Lys
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Arg Ile His Glu Ala Tyr Leu Lys Asn Phe Asn Met Asn Lys Val Lys
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Lys Met Val Ala Asn Gly Val Glu Asp Lys Glu Ala Glu Val Arg Phe
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Gln Val Thr Leu Leu Lys Tyr Gly Val Tyr Glu Ala Ile Phe Thr Met
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Gly Phe Ile Thr Arg Glu Phe Leu Lys Asn Leu Arg Lys Pro Phe Cys
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Asp Ile Met Glu Pro Lys Phe Asp Phe Ala Met Lys Phe Asn Ala Leu
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Cys Gly Asp Arg Pro Gly Leu Leu Asn Ile Gly Tyr Ile Glu Lys Leu
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 Glu His Thr Leu Pro Ser Ser Ser Cys Ala Asp Leu Ser Gln Asn Ser  
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 Ser Pro Ser Ser Leu Leu Asp Gln Leu Gln Met Gly Cys Asp Gly Ala  
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 Gly Arg Met Pro Asp Gly Glu Lys Arg Lys Leu Val Ala Gly Leu Thr  
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-22-

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Ser Val His Val Phe Tyr Arg Cys Gln Ser Thr Thr Val Glu Thr Val	
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cga gag ctc acc gag ttc gcc aag aac atc ccc aac ttc agc agc ctc	816
Arg Glu Leu Thr Glu Phe Ala Lys Asn Ile Pro Asn Phe Ser Ser Leu	
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ttc ctc aat gac cag gtg acc ctc ctc aag tat ggc gtg cac gag gcc	864
Phe Leu Asn Asp Gln Val Thr Leu Leu Lys Tyr Gly Val His Glu Ala	
275 280 285	
atc ttt gcc atg ctg gcc tcc atc gtc aac aaa gac ggg ctg ctg gtg	912
Ile Phe Ala Met Leu Ala Ser Ile Val Asn Lys Asp Gly Leu Leu Val	
290 295 300	
gcc aac ggc agt ggc ttc gtc acc cac gag ttc ttg cga agt ctc cgc	960
Ala Asn Gly Ser Gly Phe Val Thr His Glu Phe Leu Arg Ser Leu Arg	
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aag ccc ttc agt gac atc att gag ccc aag ttc gag ttt gct gtc aag	1008
Lys Pro Phe Ser Asp Ile Ile Glu Pro Lys Phe Glu Phe Ala Val Lys	
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Phe Asn Ala Leu Glu Leu Asp Asp Ser Asp Leu Ala Leu Phe Ile Ala	
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Ala Ile Ile Leu Cys Gly Asp Arg Pro Gly Leu Met Asn Val Pro Gln	
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gta gaa gcc atc cag gac acc att ctg cgg gct cta gaa ttc cat ctg	1152
Val Glu Ala Ile Gln Asp Thr Ile Leu Arg Ala Leu Glu Phe His Leu	
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Gln Val Asn His Pro Asp Ser Gln Tyr Leu Phe Pro Lys Leu Leu Gln	
385 390 395 400	
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Lys Met Ala Asp Leu Arg Gln Leu Val Thr Glu His Ala Gln Met Met	
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cag tgg cta aag aag acg gag agt gag acc ttg ctg cac ccc ctg ctc	1296
Gln Trp Leu Lys Lys Thr Glu Ser Glu Thr Leu Leu His Pro Leu Leu	
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Gln Glu Ile Tyr Lys Asp Met Tyr *	

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435

440

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 <213> Mus musculus

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Glu	His	Thr	Leu	Pro	Ser	Ser	Ser	Cys	Ala	Asp	Leu	Ser	Gln	Asn	Ser
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Ser	Pro	Ser	Ser	Leu	Leu	Asp	Gln	Leu	Gln	Met	Gly	Cys	Asp	Gly	Ala
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Ser	Gly	Phe	His	Tyr	Gly	Val	His	Ala	Cys	Glu	Gly	Cys	Lys	Gly	Phe
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Phe	Arg	Arg	Thr	Ile	Arg	Met	Lys	Leu	Glu	Tyr	Glu	Lys	Cys	Asp	Arg
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Ile	Cys	Lys	Ile	Gln	Lys	Lys	Asn	Arg	Asn	Lys	Cys	Gln	Tyr	Cys	Arg
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Ala	Ser	Glu	Gly	Cys	Gln	His	Asn	Pro	Gln	Leu	Ala	Asp	Leu	Lys	Ala
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Phe	Ser	Lys	His	Ile	Tyr	Asn	Ala	Tyr	Leu	Lys	Asn	Phe	Asn	Met	Thr
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Pro	Phe	Val	Ile	His	Asp	Ile	Glu	Thr	Leu	Trp	Gln	Ala	Glu	Lys	Gly
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Leu	Val	Trp	Lys	Gln	Leu	Val	Asn	Gly	Leu	Pro	Pro	Tyr	Asn	Glu	Ile
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Ser	Val	His	Val	Phe	Tyr	Arg	Cys	Gln	Ser	Thr	Thr	Val	Glu	Thr	Val
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Phe	Asn	Ala	Leu	Glu	Leu	Asp	Asp	Ser	Asp	Leu	Ala	Leu	Phe	Ile	Ala
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Ala	Ile	Ile	Leu	Cys	Gly	Asp	Arg	Pro	Gly	Leu	Met	Asn	Val	Pro	Gln
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Val	Glu	Ala	Ile	Gln	Asp	Thr	Ile	Leu	Arg	Ala	Leu	Glu	Phe	His	Leu
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Gln	Val	Asn	His	Pro	Asp	Ser	Gln	Tyr	Leu	Phe	Pro	Lys	Leu	Leu	Gln
	385				390					395				400	
Lys	Met	Ala	Asp	Leu	Arg	Gln	Leu	Val	Thr	Glu	His	Ala	Gln	Met	Met
			405					410						415	
Gln	Trp	Leu	Lys	Lys	Thr	Glu	Ser	Glu	Thr	Leu	Leu	His	Pro	Leu	Leu
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 tgaccactct tgttagccca agttgaagaa agccgggctg tgcctgggag ccgagagagg 240  
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 Met Tyr  
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gga aat tat tct cac ttc atg aag ttt ccc gca ggc tat gga ggc tcc 345  
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cct ggc cac act ggc tct aca tcc atg agc cca tca gca gcc ttg tcc 393  
 Pro Gly His Thr Gly Ser Thr Ser Met Ser Pro Ser Ala Ala Leu Ser  
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 Thr Gly Lys Pro Met Asp Ser His Pro Ser Tyr Thr Asp Thr Pro Val  
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ggc tct cca tat cga gtc atc acc tct gcc atg ggc cca ccc tca gga 537  
 Gly Ser Pro Tyr Arg Val Ile Thr Ser Ala Met Gly Pro Pro Ser Gly  
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gca ctt gca gcg cct cca gga atc aac ttg gtt gcc cca ccc agc tct 585  
 Ala Leu Ala Ala Pro Pro Gly Ile Asn Leu Val Ala Pro Pro Ser Ser  
 85 90 95

cag cta aat gtg gtc aac agt gtc agc agt tca gag gac atc aag ccc 633  
 Gln Leu Asn Val Val Asn Ser Val Ser Ser Ser Glu Asp Ile Lys Pro  
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tta cca ggg ctt ccc ggg att gga aac atg aac tac cca tcc acc agc 681  
 Leu Pro Gly Leu Pro Gly Ile Gly Asn Met Asn Tyr Pro Ser Thr Ser  
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ccc gga tct ctg gtt aaa cac atc tgt gcc atc tgt gga gac aga tcc 729  
 Pro Gly Ser Leu Val Lys His Ile Cys Ala Ile Cys Gly Asp Arg Ser  
 135 140 145

tca gga aag cac tac ggg gta tac agt tgt gaa ggc tgc aaa ggg ttc 777  
 Ser Gly Lys His Tyr Gly Val Tyr Ser Cys Glu Gly Cys Lys Gly Phe  
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ttc aag agg acg ata agg aag gac ctc atc tac acg tgt cgg gat aat 825  
 Phe Lys Arg Thr Ile Arg Lys Asp Leu Ile Tyr Thr Cys Arg Asp Asn  
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aaa gac tgc ctc att gac aag cgt cag cgc aac cgc tgc cag tac tgt 873



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Arg 195	Tyr	Gln	Lys	Cys	Leu 200	Val	Met	Gly	Met	Lys 205	Arg	Glu	Ala	Val	Gln 210	
gaa	gaa	aga	cag	agg	agc	cga	gag	cga	gct	gag	agt	gag	gca	gaa	tgt	969
Glu	Glu	Arg	Gln	Arg	Ser 215	Arg	Glu	Arg	Ala 220	Glu	Ser	Glu	Ala	Glu	Cys 225	
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Ala	Thr	Ser	Gly	His	Glu	Asp	Met	Pro 235	Val	Glu	Arg	Ile	Leu 240	Glu	Ala	
gaa	ctt	gct	gtt	gaa	cca	aag	aca	gaa	tcc	tat	ggg	gac	atg	aat	atg	1065
Glu	Leu	Ala	Val	Glu	Pro	Lys 245	Thr	Glu	Ser	Tyr	Gly	Asp	Met	Asn	Met	
gag	aac	tcg	aca	aat	gac	cct	gtt	acc	aac	ata	tgt	cat	gct	gct	gac	1113
Glu	Asn	Ser	Thr	Asn	Asp	Pro 260	Val	Thr	Asn	Ile	Cys 265	His	Ala	Ala	Asp	
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Lys 275	Gln	Leu	Phe	Thr	Leu 280	Val	Glu	Trp	Ala	Lys 285	Arg	Ile	Pro	His	Phe 290	
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Ser	Asp	Leu	Thr	Leu 295	Glu	Asp	Gln	Val	Ile 300	Leu	Leu	Arg	Ala	Gly	Trp 305	
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Asp	Gly	Ile	Leu	Leu	Ala	Thr 325	Gly	Leu	His	Val	His	Arg	Ser	Ser	Ala	
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His	Ser	Ala	Gly	Val	Gly	Ser 340	Ile	Phe	Asp	Arg	Val 345	Leu	Thr	Glu	Leu	
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Val	Ser	Lys	Met	Lys	Asp 355	Met	Gln	Met	Asp	Lys 360	Ser	Glu	Leu	Gly	Cys 365	
ctg	cga	gcc	att	gta	ctc	ttt	aac	cca	gat	gcc	aag	ggc	ctg	tcc	aac	1449
Leu	Arg	Ala	Ile	Val 375	Leu	Phe	Asn	Pro	Asp 380	Ala	Lys	Gly	Leu	Ser	Asn	
ccc	tct	gag	gtg	gag	act	ctg	cga	gag	aag	gtt	tat	gcc	acc	ctt	gag	1497
Pro	Ser	Glu	Val	Glu	Thr	Leu	Arg	Glu 390	Lys	Val	Tyr	Ala	Thr	Leu	Glu	
gcc	tac	acc	aag	cag	aag	tat	ccg	gaa	cag	cca	ggc	agg	ttt	gcc	aag	1545
Ala	Tyr	Thr	Lys	Gln	Lys	Tyr 405	Pro	Glu	Gln	Pro	Gly	Arg	Phe	Ala	Lys	
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Leu	Leu	Leu	Arg	Leu	Pro	Ala 420	Leu	Arg	Ser	Ile	Gly 425	Leu	Lys	Cys	Leu	
gag	cac	ctc	ttc	ttc	ttc	aag	ctc	atc	ggg	gac	acc	ccc	att	gac	acc	1641
Glu	His	Leu	Phe	Phe	Phe 435	Lys	Leu	Ile	Gly	Asp 440	Thr	Pro	Ile	Asp	Thr 445	

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ttc ctc atg gag atg ttg gag acc ccg ctg cag atc acc tga 1683  
 Phe Leu Met Glu Met Leu Glu Thr Pro Leu Gln Ile Thr \*  
 455 460

gccccaccag ccacagcctc cccacccagg atgacccctg ggcaggtgtg tgtggacccc 1743  
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 <213> Homo Sapien

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 Pro Val Ser Ala Pro Arg Thr Leu Ser Ala Val Gly Thr Pro Leu Asn  
 50 55 60  
 Ala Leu Gly Ser Pro Tyr Arg Val Ile Thr Ser Ala Met Gly Pro Pro  
 65 70 75 80  
 Ser Gly Ala Leu Ala Ala Pro Pro Gly Ile Asn Leu Val Ala Pro Pro  
 85 90 95  
 Ser Ser Gln Leu Asn Val Val Asn Ser Val Ser Ser Ser Glu Asp Ile  
 100 105 110  
 Lys Pro Leu Pro Gly Leu Pro Gly Ile Gly Asn Met Asn Tyr Pro Ser  
 115 120 125  
 Thr Ser Pro Gly Ser Leu Val Lys His Ile Cys Ala Ile Cys Gly Asp  
 130 135 140  
 Arg Ser Ser Gly Lys His Tyr Gly Val Tyr Ser Cys Glu Gly Cys Lys  
 145 150 155 160  
 Gly Phe Phe Lys Arg Thr Ile Arg Lys Asp Leu Ile Tyr Thr Cys Arg  
 165 170 175  
 Asp Asn Lys Asp Cys Leu Ile Asp Lys Arg Gln Arg Asn Arg Cys Gln  
 180 185 190  
 Tyr Cys Arg Tyr Gln Lys Cys Leu Val Met Gly Met Lys Arg Glu Ala  
 195 200 205  
 Val Gln Glu Glu Arg Gln Arg Ser Arg Glu Arg Ala Glu Ser Glu Ala  
 210 215 220  
 Glu Cys Ala Thr Ser Gly His Glu Asp Met Pro Val Glu Arg Ile Leu  
 225 230 235 240  
 Glu Ala Glu Leu Ala Val Glu Pro Lys Thr Glu Ser Tyr Gly Asp Met  
 245 250 255  
 Asn Met Glu Asn Ser Thr Asn Asp Pro Val Thr Asn Ile Cys His Ala  
 260 265 270  
 Ala Asp Lys Gln Leu Phe Thr Leu Val Glu Trp Ala Lys Arg Ile Pro  
 275 280 285  
 His Phe Ser Asp Leu Thr Leu Glu Asp Gln Val Ile Leu Leu Arg Ala  
 290 295 300  
 Gly Trp Asn Glu Leu Leu Ile Ala Ser Phe Ser His Arg Ser Val Ser  
 305 310 315 320  
 Val Gln Asp Gly Ile Leu Leu Ala Thr Gly Leu His Val His Arg Ser  
 325 330 335  
 Ser Ala His Ser Ala Gly Val Gly Ser Ile Phe Asp Arg Val Leu Thr  
 340 345 350  
 Glu Leu Val Ser Lys Met Lys Asp Met Gln Met Asp Lys Ser Glu Leu  
 355 360 365  
 Gly Cys Leu Arg Ala Ile Val Leu Phe Asn Pro Asp Ala Lys Gly Leu  
 370 375 380  
 Ser Asn Pro Ser Glu Val Glu Thr Leu Arg Glu Lys Val Tyr Ala Thr  
 385 390 395 400  
 Leu Glu Ala Tyr Thr Lys Gln Lys Tyr Pro Glu Gln Pro Gly Arg Phe  
 405 410 415  
 Ala Lys Leu Leu Leu Arg Leu Pro Ala Leu Arg Ser Ile Gly Leu Lys

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Cys	Leu	Glu	His	Leu	Phe	Phe	Phe	Lys	Leu	Ile	Gly	Asp	Thr	Pro	Ile
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						Ile											
						Thr											
						Ser											
						5											
gtg	aca	ttc	tgc	ttc	cca	ata	162										
Val	Thr	Phe	Cys	Phe	Pro	Ile											
			10														
cca	tcc	cag	att	aac	tca	aca	210										
Pro	Ser	Gln	Ile	Asn	Ser	Thr											
		25				Val											
						30											
ccc	cct	gaa	gat	gtg	aag	cca	258										
Pro	Pro	Glu	Asp	Val	Lys	Pro											
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tgt	cca	ccc	cct	cca	ggt	ggc	306										
Cys	Pro	Pro	Pro	Pro	Gly	Gly											
	55				60												
atc	tgc	ggg	gac	aga	agc	tca	354										
Ile	Cys	Gly	Asp	Arg	Ser	Ser											
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gag	ggt	tgc	aag	ggc	ttc	ttc	402										
Glu	Gly	Cys	Lys	Gly	Phe	Phe											
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tac	tct	tgc	cgg	gac	aac	aaa	450										
Tyr	Ser	Cys	Arg	Asp	Asn	Lys											
		105				110											
aac	cgc	tgt	cag	tac	tgc	cgc	498										
Asn	Arg	Cys	Gln	Tyr	Cys	Arg											
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Lys	Arg	Glu	Ala	Val	Gln	Glu											
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ggg	gat	ggg	gag	ggg	gct	ggg	594										
Gly	Asp	Gly	Glu	Gly	Ala	Gly											
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ggg gtc aat cca ctc tcc ttc gtg atg ggg gtt ggg gga ggc agt cta 738  
 Gly Val Asn Pro Leu Ser Phe Val Met Gly Val Gly Gly Gly Ser Leu  
 200 205 210

ggt ctg ttc tac atc ccc tcc ccc tcc ttt ccc ctc ata acc ttc cta 786  
 Gly Leu Phe Tyr Ile Pro Ser Pro Ser Phe Pro Leu Ile Thr Phe Leu  
 215 220 225 230

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 235 240 245

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 50 55 60  
 Gly Lys Arg Leu Cys Ala Ile Cys Gly Asp Arg Ser Ser Gly Lys His  
 65 70 75 80  
 Tyr Gly Val Tyr Ser Cys Glu Gly Cys Lys Gly Phe Phe Lys Arg Thr  
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 Ile Arg Lys Asp Leu Thr Tyr Ser Cys Arg Asp Asn Lys Asp Cys Thr  
 100 105 110  
 Val Asp Lys Arg Gln Arg Asn Arg Cys Gln Tyr Cys Arg Tyr Gln Lys  
 115 120 125  
 Cys Leu Ala Thr Gly Met Lys Arg Glu Ala Val Gln Glu Glu Arg Gln  
 130 135 140  
 Arg Gly Lys Asp Lys Asp Gly Asp Gly Glu Gly Ala Gly Ala Pro  
 145 150 155 160  
 Glu Glu Met Pro Val Asp Arg Ile Leu Glu Ala Glu Leu Ala Val Glu  
 165 170 175  
 Gln Lys Ser Asp Gln Gly Val Glu Gly Pro Gly Gly Thr Gly Gly Ser  
 180 185 190  
 Gly Ser Ser Val Ser Val Gly Val Asn Pro Leu Ser Phe Val Met Gly  
 195 200 205  
 Val Gly Gly Gly Ser Leu Gly Leu Phe Tyr Ile Pro Ser Pro Ser Phe  
 210 215 220  
 Pro Leu Ile Thr Phe Leu Thr Leu Leu Gly Thr Gly Gly Ala Ala Lys